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THE FAMILIAL OCCURRENCE OF INFANTILE CORTICAL HYPEROSTOSIS IN UTERO

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SINCE the initial reports of Caffey and Silverman[1] and Smyth, Potter, and Silverman[2] of a syndrome which has come to be known as "infantile cortical hyperostosis," its etiology has been subject to considerable speculation. It is desirable therefore that observations, which discount some speculations and may shed light on others, be reported. We are, therefore, presenting this report of our observations of the familial occurrence of this disorder in two siblings who presented manifestations in utero. A dynamic concept of the pathogenesis will be presented as a consequence of our experiences.

Classically, infantile cortical hyperostosis may have its onset any time during the last month in utero and the first seven months of life. It is characterized by the development of brawny, tender, nonhyperemic, nonsuppurative swelling over one or more bones followed by the development of underlying cortical hyperostoses. The hyperostosis can be demonstrated by roentgenograms up to twelve months after the soft tissue findings disappear. Irritability is prominent so long as tenderness prevails. The course is typical only in the extreme variability of its duration and the frequent occurrence of remissions and exacerbations. New lesions rarely develop after the first year of life and in some cases the entire course is only three months long. Frequently lesions will clear and then recur at the same site or sites, or while one group of lesions are subsiding others will be developing elsewhere.

The hyperostoses are limited to the diaphysis by roentgenogram and never involve the epiphysis or metaphysis. Initially they appear as irregular cortical thickenings. Later they may become lamellated as healing occurs. Subclinical hyperostoses, detectable only by roentgenogram, occur. The mandible, long bones, and ribs are most frequently involved. However, involvement of all bones except the vertebrae and phalanges has been reported.

The other abnormal findings noted commonly, but not invariably, during the periods of local tenderness and irritability are fever, elevation of the erythrocyte sedimentation rate and the serum alkaline phosphatase, pallor, pseudoparalysis, and, less commonly, pleural effusion in association with lesions of the ribs. It should be noted that fever is uncommon in early

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infancy. Anemia has been associated with several cases. The differential leukocyte count generally reveals a mild lymphocytosis, but eosinophilia and neutrophilia have been reported. Reviews by Caffey[3] and Racely, Bilderback, and Burton[4] give more detailed discussions of this syndrome and its many variations.

CASE REPORTS

CASE 1.—K. B. (370-486), white female infant, was born June 27, 1950, at the MacNeal Memorial Hospital with brawny, tender, nonhyperemic, fusiform swellings of both arms and legs and less marked swellings over both angles of the mandible, the clavicles, and two ribs. Hyperostoses could be palpated under the soft tissue swellings. The arms were held flexed and externally rotated. There was a painful pseudoparesis of all four extremities and passive movement caused marked pain. The infant was very irritable. There was no fever at any time during the course. Progress was satisfactory in all other respects. The infant fed well; she weighed 3,118 grams, 56 grams over her birth weight, on July 7, 1950, when she was transferred to the Research and Educational Hospitals for further evaluation. Physical examination revealed no abnormalities other than those noted above.

The mother's prenatal course was uneventful except for mild nausea and vomiting during the first trimester. The maternal Wassermann test was negative. The mother took 15 grains of ferrous sulfate, calcium, and supplemental vitamins including 10,000 international units of vitamin A per day during her pregnancy. Delivery was uneventful after a nine-hour labor. A prenatal film taken one week before delivery had been interpreted as showing bony abnormalities in the legs and arms of the fetus (see Fig. 1).

Roentgenograms revealed irregular cortical thickenings of the mandible, clavicles, radii, ulnas, several ribs, tibias, and fibulas, limited to the diaphysis in the tubular bones (see Fig. 2). Other studies were as follows: The nose and throat cultures revealed *E. coli*. The urinalysis was negative. Hemoglobin was 14.5 grams per cent and hematocrit 43 per cent. There were 9,300 leukocytes per cubic millimeter. The differential leukocyte count was normal. The erythrocyte sedimentation rate (Wintrobe) was zero millimeters in the first hour. The Wassermann and Kahn test were negative. The serum phosphorus was 6.8 mg. per cent, calcium 9.7 mg. per cent, alkaline phosphatase 20.6 Bodansky units, nonprotein nitrogen 44 mg. per cent, uric acid 2.4 mg. per cent. The whole blood vitamin C was 0.5 mg. per cent. The plasma vitamin A was 42.7 μg. per cent and the plasma carotene was 37.9 μg per cent. Intradermal skin tests for tuberculosis, histoplasmosis, coccidiomycosis, and blastomycosis were negative.

A diagnosis of infantile cortical hyperostosis was made and no treatment instituted other than usual well-baby care and careful observation. The course was an unusually severe and protracted one, with several fresh lesions appearing as some of the older ones cleared in the same or new sites until the child was 17 months old. All the hyperostoses have not resolved as yet. The persistence of the painful lesions in the legs resulted in a prolonged pseudoparesis so that standing and walking were delayed till age 15 months and 19 months, respectively. Marked demineralization of the bones of the legs developed which may be attributable to pseudoparesis with disuse atrophy (see Fig. 3). There has been considerable improvement in the bone mineralization since the child started to walk. Marked anterior bowing of the tibias developed and persists although considerable improvement has occurred since the the child started to walk (see Fig.

Fig. 1.—Prenatal roentgenograms showing bony abnormalities of fetal tibias, fibulas, and less clearly of one radius in Case 1 (K. B.).

4). Very marked ulnar deviation occurred bilaterally which corrected spontaneously as the forearm lesions became inactive. The child has been well since age 18 months except for asymptomatic anterior bowing of the tibias and now has normal neuromuscular development.

Fig. 2.—Roentgenograms of K. B. when 13 days old.

CASE 2.—M. B., white male infant, the brother of K. B. (Case 1), was born at the MacNeal Memorial Hospital on May 31, 1952, after a normal prenatal course similar in all respects to that recorded above for his sibling. At delivery a tender, brawny, nonhyperemic, nonsuppurative swelling was noted over the anterior half of the right leg. Under the soft tissue swelling a bony hyperostosis was palpated. A prenatal roentgenogram taken five weeks before delivery showed a bony abnormality in one fetal leg (see Fig. 5). The infant was otherwise normal and weighed 3,657 grams. His weight progress was normal and he was

Fig. 3.—Roentgenograms of Case 1 (K. B.) at age 10 months showing marked anterior bowing and demineralization.

Fig. 4.—Roentgenogram of Case 1 (K. B.) at age 25 months showing remineralization and reorganization of bones with some improvement in anterior bowing.

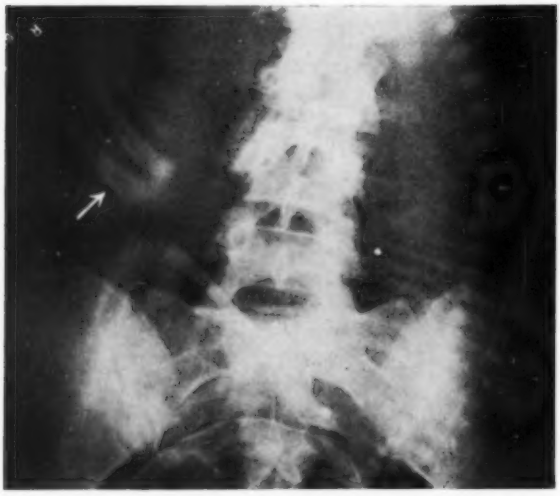

Fig. 5.—Prenatal roentgenogram in Case 2 (M. B.) with arrow indicating hyperostosis of one tibia.

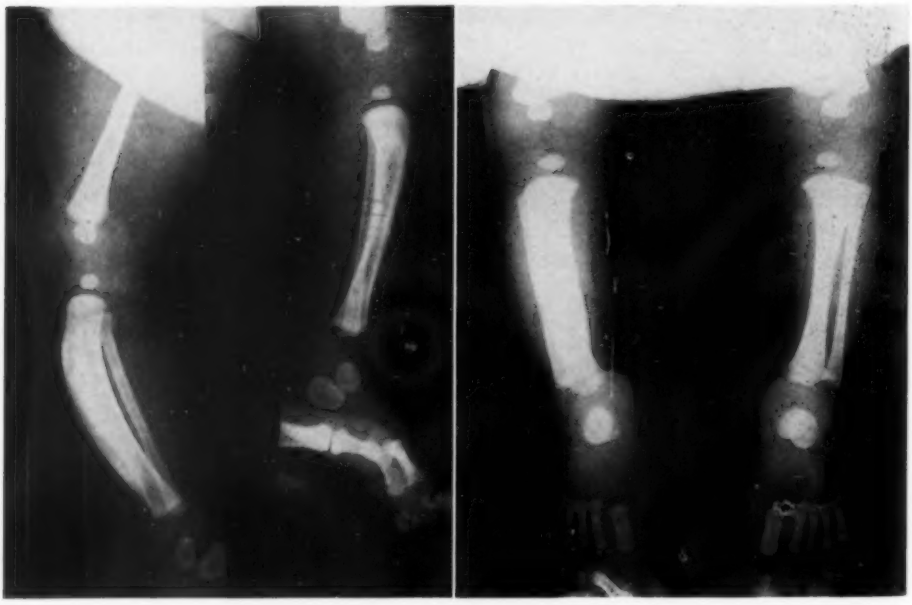

Fig. 6.—Roentgenograms of hyperostosis in Case 2 (M. B.) at 12 days of age.

transferred to Research and Educational Hospitals on June 10, 1952, for further study.

Physical examination on admission revealed an irritable infant with the findings mentioned above in the right leg. In addition, a painful pseudoparesis and anterior bowing of the involved leg were present.

Roentgenograms failed to reveal any lesions other than the irregular cortical thickening of the right tibia (see Fig. 6). The erythrocyte sedimentation rate (Wintrobe) was 22 mm. in one hour. The hemoglobin was 13 grams per cent. The leukocyte count was 14,200 per cubic millimeter. The differential leukocyte count was within normal limits. The serum calcium and phosphorus were 9.0 and 8.1 mg. per cent, respectively. The alkaline phosphatase was 4.6 Bodansky units. The Wassermann and Kahn tests were negative.

A diagnosis of infantile cortical hyperostosis was made. It was decided to administer ACTH experimentally to this infant. Bush and Merrell[5] reported the use of ACTH in this disease and noted the prompt subsidence of the clinical symptoms during and after eight days of adequate dosage, although the bone lesions did not clear until four months later. It was felt that in their case the subsidence of the symptoms may have been coincidental with the administration of ACTH or that it might represent the well-known nonspecific effect of the hormone on any fibroblastic type of reaction. The latter would be in keeping with their observations, as the soft tissue changes appear to be secondary to atrophy, and fibrosis. No inflammatory changes occur in the bone. There is some experimental evidence that ACTH has a direct effect on osteogenesis and chondrogenesis.[6, 7] However, the extreme variations in the natural clinical course make it impossible to judge therapy on the basis of one case.

Accordingly, this infant was given ACTH at a dosage adequate to reduce the eosinophil count to near zero for one week. Forty-eight hours after the hormone was started the tenderness disappeared. During the week there was a definite diminution in the amount of soft tissue swelling. The infant's irritability disappeared. There were no manifestations of ACTH side effects except that the infant failed to gain weight while getting the hormone. Normal weight gain began forty-eight hours after hormone therapy was discontinued. There has been no recurrence of the pain and swelling. No new lesions have developed during the subsequent two months.

DISCUSSION

The etiology of this syndrome remains a mystery. It is interesting to speculate on the possibilities. Caffey[3] has chosen to classify this as an infection of the skeletal system although admitting that there is little supporting evidence for this speculation. Attempts to incriminate bacteria[2, 9-11] and viruses[8] as etiological factors have been unsucessful. Few biopsies have included more than superficial spicules of bone. Therefore the histological reports are not entirely satisfactory, but have failed to reveal the presence of inflammatory reaction in the bone, periosteum, or soft tissues.[2, 9-13]

Mossberger[10] described the bone pathology of infantile cortical hyperostosis in an infant whose cause of sudden death was unknown. He did not find any evidence of inflammation. He noted that there were two layers of spongy bone which represented the cortex of the diaphysis with no compact bone present. The inner of these layers seemed to represent the origi-

nal shaft. It was formed by trabeculae with a layer of new bone on their surface and surrounded by an incomplete layer of osteoblasts. Marrow was present in the Haversian spaces. The outer layer was scantily vascularized and the Haversian spaces contained loose fibrillary tissue. The trabeculae were covered with a complete layer of osteoblasts. The periosteum was thickened by many fibrocytes and collagen fibrils and scattered below it were osteoclasts. Interrupting the epiphyseal line were microscopic strands of connective tissue containing trabeculae of bone and cartilage running from the diaphysis. The lacunar arrangement was distorted only in the immediate vicinity of these strands. These findings are compatible with the reports of biopsies in so far as comparable tissue has been examined.

The occurrence of the disease in utero has been cited above. Kitchin[14] reported the disease in an infant aged 6 hours, which must have originated in utero, and there was a history of a similar lesion in the mother. Van Zeben[11] reported three cases in one family. These reports, combined with the pathological studies and the failure to respond to any type of antibiotic or chemotherapy,[4] make an infectious-inflammatory origin of this disease very unlikely.

Mossberger[10] suggested that this disease represents excessive embryonal osteogenesis. Re-evaluation of the minimal available data would suggest that embryonal osteodysgenesis would be a better term. It is of interest that the lesions of infantile cortical hyperostosis have been recorded in a variety of sites which approximate the location of the primary centers of ossification in a fetus nine weeks or slightly older.[15] The appendicular musculature becomes completely differentiated and functional during the second and third fetal months. There is a period of very rapid growth of the extremities during the third fetal month terminating in a 90 degree rotation to the normal human position. The combination of the factors of rapid growth, preliminary ossification, muscle pull, and change in relationships may lead to a certain amount of distortion of the bone.

Primary ossification consists of the more or less simultaneous development of enchondral and perichondral bone formation. The latter forms a splint around the shaft weakened at the zones of cartilage, destruction occurring with enchondral bone formation. The fetal periostium is proportionately much thicker than that of well-developed bone, resembling that described over the lesions of infantile cortical hyperostosis. Normal bone formation requires excellent vascularization at the site of ossification.

The many cellular and physicochemical changes associated with the gross changes in osteogenesis have been reviewed by Robinson.[16] The factors controlling these phenomena are not clearly defined.

The histological picture seen in infantile cortical hyperostosis suggests that the rapid development and in some instances subsequent distortion of the fetal bone results in an inadequate vascular supply to the involved bone. As a result, there is a failure of normal perichondral bone formation. A compensatory increase in endosteal bone formation follows at

a later date. This is bizarre in form as it is structurally inappropriate for the stresses and strains normally brought to bear on cortical bone and also suffers from an inadequate blood supply. The lamellated appearance of these lesions late in their course would occur with the uneven resumption of periosteal bone formation when the blood supply and other controlling factors are adequate for same to occur.

The changes in the soft tissue are those of atrophy and fibrosis which are also compatible with an inadequate blood supply. It is necessary to hypothesize that the arrest in osteogenesis persists in many sites until the blood supply and/or other controlling factors become adequate for the aberrant compensatory endosteal bone formation to occur followed by the resumption of periosteal bone formation some weeks or months after birth.

The pain and tenderness noted during the acute phase of the development of these lesions may be due to the stretching of the periostium by the mass of aberrant cancellous bone or secondary to atrophic changes resulting from the period of avascularity.

Retrospective evaluation of the studies reported in this disease has served to highlight the need of utilizing modern techniques in the study of bone disease. Robinson[16] has demonstrated that the formation of hydroxyapatite crystals in normal bone matrix results in a hexagonal tabular crystal whereas those crystals formed in abnormal matrix seem to have different shapes. Follis[17, 18] has discussed histochemical techniques which might be of great help in defining more clearly the defects in osteogenesis present in this disease.

The familial occurrence of this syndrome, the onset in fetal life at the earliest and rarely after 7 months of age, has raised the question of a possible relationship to the changes in endocrine function occurring during this period. It has been noteworthy that all reports of this disease have failed to mention any disturbance in epiphyseal or metaphyseal growth. In contrast to this observation, all known hormones affecting bone growth exert their greatest effect at the epiphysis or metaphysis. It is unlikely that a humoral agent would produce intermittently occurring local lesions over a period as long as a year.

In spite of these facts, which make a disturbance in endocrine function as the primary etiological agent exceedingly unlikely, the preliminary observations of a questionable response to ACTH necessitates further investigation. It must be remembered that the use of ACTH in this age group is hazardous. There is an increased risk of infection and of profound electrolyte disturbances. The use of ACTH in this self-limited disease is not warranted at this time except under carefully controlled experimental conditions.

The cases cited above demonstrate the occurrence of this disease in utero. They indicate a need to examine all prenatal roentgenograms carefully to determine how early such changes can be demonstrated and if perhaps some cases occur and heal before the end of the fetal period. Careful study of fetuses and stillbirths should provide material to

document in greater detail the pathogenesis of this disease.

It is apparent from the evidence reviewed that infantile cortical hyperostosis is probably not an infectious disease. While the evidence is not entirely clear, there is no indication that a disturbance in endocrine function can be incriminated as an etiological factor. There is only one case to suggest that this is a hereditary defect.[14] In contrast, the occurrence in utero, the familial occurrence, the histological studies and the natural history of the syndrome indicate that there is a local factor interfering with normal bone development. It is postulated that this is a defect in vascular supply to the fetal diaphysis occurring during the third month of fetal life and resulting in embryonal osteodysgenesis.

SUMMARY

The history, clinical findings, roentgenographic changes, and pathological studies of infantile cortical hyperostosis were summarized. Two cases of infantile cortical hyperostosis occurring in sibling and demonstrated on utero by prenatal roentgenograms were presented. Evidence that this syndrome is not infectious in nature and that the cortical thickening is not cortical bone has been reviewed. A hypothetical explanation of the pathogenesis of the syndrome is presented. Several directions of further investigation are suggested.

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CHLOROMYCETIN PALMITATE

Observations on Absorption, Blood Serum Levels, and Urinary Excretion

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THE value of Chloromycetin in the treatment of infections due to most bacteria, the pathogenic rickettsiae, and many of the large viruses has now been well established. Because of the bitterness of the crystalline compound, its usefulness has been limited in some instances by the practical problem of administration. The use of the encapsulated drug met most of the therapeutic problems; however, many children and occasionally adults did not accept capsules readily. This need for a more palatable oral preparation of Chloromycetin stimulated the investigation of certain insoluble tasteless Chloromycetin derivatives. These studies led to the preparation of Chloromycetin Palmitate (combining Chloromycetin and palmitic acid) from which free Chloromycetin could be liberated in the intestinal tract by enzyme hydrolysis. The main factors determining the rate and degree of hydrolysis are emulsification by bile and the splitting action of intestinal lipases.[1]

The palmitic acid ester of Chloromycetin* was made available for this study. It was supplied as a custard-flavored suspension of Chloromycetin Palmitate containing 125 mg. of Chloromycetin base per 4.0 c.c. The use of this product in children has been reported to be well tolerated and therapeutically effective.[2, 3, 4]

PURPOSE

This study was planned to determine (1) the palatability and patient acceptance of Chloromycetin Palmitate Suspension by children and adults, (2) the time of peak serum levels following the administration of single doses, (3) the duration of serum levels, (4) serum levels in patients receiving multiple doses, and (5) the urinary excretion rate during the first twenty-four hours. All dose calculations were made in terms of Chloromycetin equivalent (125 mg. Chloromycetin per each 4.0 c.c.).

METHODS OF STUDY

A total of seventeen children was selected at random from hospitalized patients who were moderately ill or convalescing from acute infectious processes. Immediately following withdrawal of a control blood specimen, single oral doses of Chloromycetin Palmitate Suspension were administered to ten children without dietary restrictions. Subsequent blood specimens were taken at one-, three-, four-, eight-, twelve-, and twenty-four-hour intervals thereafter. The ages of this group ranged from 1 month to 11 years and the drug dosage used was from 36 to 100 mg. per kilogram of body weight.

Twelve children, ranging from 5 months to 12 years of age, were placed on multiple dose schedules of

From the Ben Taub Infectious Diseases Laboratory, Jefferson Davis Hospital; the Departments of Medicine and Pediatrics, Baylor University College of Medicine; and the Department of Clinical Investigation, Parke, Davis & Company.

*Pediatric Chloromycetin Palmitate Suspension was supplied by the Department of Clinical Investigation, Parke, Davis & Company, Detroit, Mich. The esterified product contains 57.6 per cent Chloromycetin.

from 30 to 144 mg. per kilogram per day, dividing the total calculated dose into 4 to 6 doses during a twenty-four-hour period. No restriction of diet was ordered. During a seven-day period of continuous drug schedule, sufficient daily blood samples were drawn to reflect the relative drug serum levels attained in this group.

Twelve adults (27 to 68 years of age), all bed patients, convalescing from a variety of illnesses, were given single oral doses of Chloromycetin Palmitate Suspension of from 5 to 40 mg. per kilogram. Blood serum levels were determined at one-, three-, six-, eight-, twelve-, twenty-four-, and forty-eight-hour intervals following the drug. Two normal adults received 50 and 100 mg. per kilogram, respectively, and were sampled at one-half-, one-, three-, seven-, eight-, eleven-, twelve-, and twenty-four-hour intervals. Urinary excretion of drug during the first twenty-four-hour period of test was estimated by the colorimetric method in eleven of these adults.

Blood specimens were allowed to clot, the serum separated, and stored at 42° F. for two to three days, or frozen if held for longer periods. Urine specimens were held at 42° F. and tested within forty-eight hours after collection.

A colorimetric method, described by Glazko and associates,[5] was employed for determining the drug concentration in serum and, in many instances, those levels were compared to levels assayed by a microbiologic method.[6*] The former method depends upon the reduction of nitrate groups with metallic zinc and subsequent diazotization: the microbiologic assay method employs a strain of *Shigella sonnei* as test organism and is based upon turbidimetric readings. Inactive degradation products of Chloromycetin are not distinguishable from active Chloromycetin by the colorimetric technique, and consequently give higher values than the turbidimetric method, particularly as the period of testing increases and the degradation products of Chloromycetin accumulate. This variance of results obtained by two methods has been discussed by other authors.[5, 7] With careful technique, either test would seem to serve as a reliable method of determining the relative amount of drug being absorbed.

*A portion of the colorimetric assays and all microbiologic assays were performed at the Research Laboratories, Parke, Davis & Company, Detroit, Mich. The majority of the colorimetric assays were done in Ben Taub Infectious Diseases Laboratory, Jefferson Davis Hospital, Houston, Texas.

RESULTS

The comparison of Chloromycetin blood levels done by colorimetric and turbidimetric methods is summarized in Fig. 1, Table I. These levels are averages of four adults who received 12 to 15 mg. per kilogram at a single dose. The Chloromycetin levels determined by the colorimetric are slightly higher than those determined by the microbiologic assays. In this series the greatest difference was 6 μg per milliliter.

In Fig. 2, Table II, blood levels following single oral doses in adults are presented. Absorption of drug is demonstrated at one hour after the dose, with peak levels occurring in the third-hour sample. A group of patients receiving 12 to 40 mg. per kilogram presented significant Chloromycetin blood levels as late as twelve

hours following the single dose of drug. Table II also shows the urinary excretion estimates to be relatively comparable following 40, 50, and 100 mg. per kilogram, indicating that excess drug may not be utilized to a maximum beyond doses of 40 to 50 mg. per kilogram.

A comparison of results following the administration of a single oral dose in children and adults (Figs. 2 and 3) suggests that adults require less drug than children on a weight basis to attain comparable drug serum levels. In general, the larger doses produce higher blood levels.

TABLE I. CHLOROMYCETIN PALMITATE, ORAL SINGLE DOSAGE TO ADULTS 12 TO 15 MG. (CHLOROMYCETIN EQUIVALENT) PER KILOGRAM

HOURS AFTER DOSAGE	1	3	6	8	12
Colorimetric	13.0 μg/ml.	11.6 μg/ml.	10.0 μg/ml.	9.6 μg/ml.	5.0 μg/ml.
Microbiologic	10.0 μg/ml.	7.0 μg/ml.	4.5 μg/ml.	3.6 μg/ml.	2.5 μg/ml.
Difference	3.0 μg/ml.	4.6 μg/ml.	5.5 μg/ml.	6.0 μg/ml.	2.5 μg/ml.

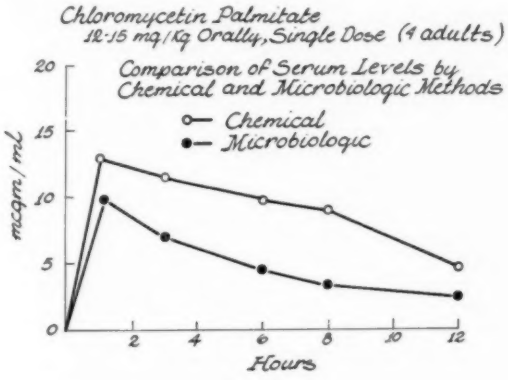

Fig. 1.

Results following administration of single doses of Chloromycetin Palmitate Suspension in children are presented in Fig. 3 and Table III. The peak levels with moderate dosage (36 to 75 mg. per kilogram) were reached by the fourth hour. A larger dose (100 mg. per kilogram) produced progressive increase in blood levels until about the eighth hour. Children receiving 75 and 100 mg. per kilogram had appreciable levels twelve hours following the administration of drug. The twelve-hour levels following doses of 36 to 50 mg. per kilogram were quite low. The administration of 100 mg. per kilogram in both children and adults tended to produce a more sustained level rather than increasing the initial peak level.

In Table IV, Fig. 4, blood levels following continuous multiple doses are recorded. Doses of from 30 to 55 mg. per kilogram per day, in divided portions, resulted in maintenance of levels which are considered to be of significant value. Relatively high serum levels follow the use of 144 mg. per kilogram per day, in divided doses, and microbiologic assays confirm the colorimetric values.

Chloromycetin Palmitate -- Serum levels following single oral dosee in adults

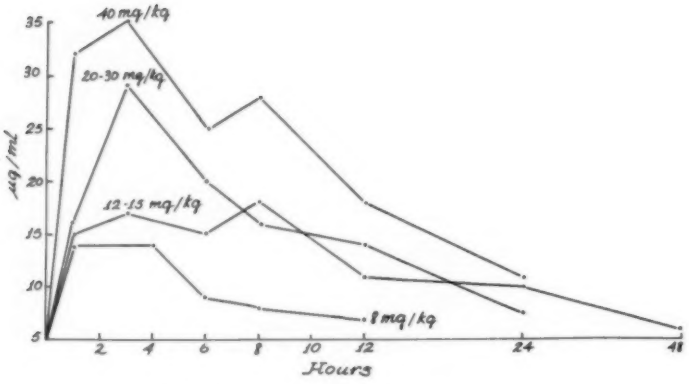

Fig. 2.

Chloromycetin Palmitate -- Serum levels following single oral doses in children.

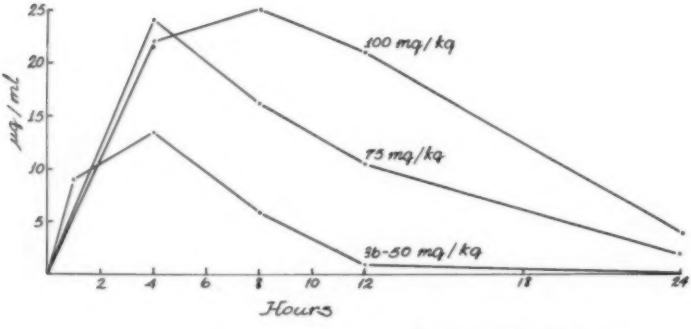

Fig. 3.

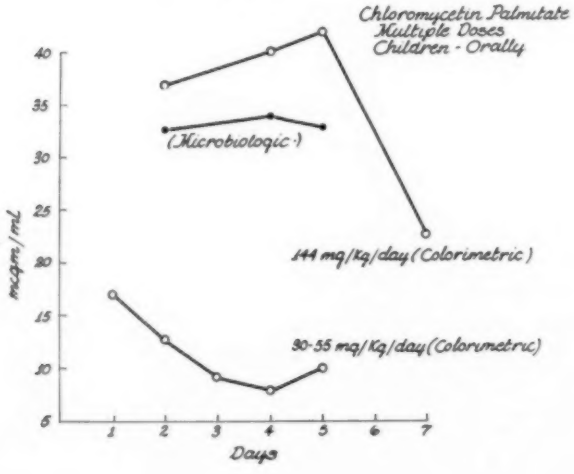

Fig. 4.

TABLE II. CHLOROMYCETIN PALMITATE, SINGLE DOSE, ORAL, TO ADULTS

PATIENT	AGE	MG./KG.	CONTROL	μG/ML. IN SERUM HOURS AFTER DOSAGE ½	1	3	6	8	12	24	48	PER CENT EXCRETED FIRST 24 HR.
L. S.	52	5	Colorimetric	x	x	x	x	x	x	x	x	x
			Microbiologic	x	4	3	3	4	0			
Sm.	36	8	Colorimetric	0	8	8	4	3	2	0	x	15.0
			Microbiologic	x	x	x	x	x	x	x	x	
B.	43	12	Colorimetric	0	5	8	8	6	4	1	1	38.0
			Microbiologic	x	x	8	x	4	3	x	x	
W.	68	15	Colorimetric	0	18	14	11	8	6			60.0
			Microbiologic	x	13	7	4	3	2	x	x	
E.	30	15	Colorimetric	0	18			14		0	x	85.0
			Microbiologic	x	x			x		x		
G.	32	15	Colorimetric	0	8	13	10	15	10	10	3	30.0
			Microbiologic	x	7	6	5	4	x	x	x	
R.	27	20	Colorimetric	0	x	29	12	10	x	2	x	67.0
			Microbiologic	x		x	x	x		x		
A.	46	25	Colorimetric	0	11	22	13	8	4	0	0	80.0
			Microbiologic	x	x	x	x	x	x	x	x	
J.	60	30	Colorimetric	0		21	21*	15	15	3	x	58.0
			Microbiologic	x	x	x	x*	x	x	x		
C.	62	40	Colorimetric	0	27	30	20	23	13	6	x	22.0
			Microbiologic	x	x	x	x	x	x	x		
E. Y.	35	50	Colorimetric	0	10	14	23		18	10	0	x	23.0
			Microbiologic	x	x	x	x	x	x	x		
H. C.	43	100	Colorimetric	0	2	2	30	32†	x	34‡	10	x	29.0
			Microbiologic	x	x	x	x	x†		x‡	x		
								Average				46.0

*5 hr. †7 hr. ‡11 hr. x—Not determined.

TABLE III. CHLOROMYCETIN PALMITATE, SINGLE DOSE, ORAL, TO CHILDREN

PATIENT	AGE	MG./KG.	CONTROL	μG/ML. IN SERUM HOURS AFTER DOSAGE 1	3	4	6	8	12	24	48
St.	1 mo.	36	0	9						x	x
Bo.	5 mo.	36	0		12/8*					x	x
Or.	3 yr.	50	0			14		2	0	0	x
Du.	7 yr.	50	0			13		10	2	0	x
Ma.	5 yr.	50	0			13		7	2	2	x
Ga.	7 yr.	75	0			36		24	16	0	x
An.	11 yr.	75	0			25		14	8	4.5	x
Wa.	2 yr.	75	0			30		19	8	2	x
Eb.	7 yr.	100	0			32		34	26	5	x
Sl.	5 yr.	100	0			13		16	16	4	x

*—Microbiolgic. Others by colorimetric. x—Not determined.

TABLE IV. CHLOROMYCETIN PALMITATE, MULTIPLE DOSE SCHEDULE, ORAL FOR CHILDREN. BLOOD SERUM LEVELS

PATIENT	AGE	WEIGHT (KG.)	DOSE SCHEDULE	MG./KG./DAY	DAYS 1	2	3	4	5	6	7
J. D.	9 yr.	25	q. 4 hr.	30	9	7.5	5.5	7.5			
N. E.	8 yr.	32	q. 6 hr.	31	5.5	6.5	11	7.5	5		
M. P.	7 yr.	21.8	q. 4 hr.	34	16	13.5	5	11.8	6.5		
S. B.	2 yr.	11.8	q. 6 hr.	42	11	6		7	7.5		
H. L.	12 yr.	34	q. 4 hr.	44.1	14	13	6	5	11		
B. E.	2 yr.	11	q. 6 hr.	45	18.5	21	25	9.5			
S. J.	20 mo.	7.3	q. 8 hr.	51	26.5	22					
B. W.	8 mo.	4.5	q. 6 hr.	55	21.5	14	7				
				Average	15.2	12.9	9.9	8	7.5		
S. P.	5 mo.	6.8	q. 6 hr.	144							23/x*
T. E.	6 mo.	5.2	q. 6 hr.	144		37/33*					
J. A. G.	1 yr.	9	q. 6 hr.	144				31/26*	31/27*		
G. A.	2 yr.	11.2	q. 6 hr.	144				49/42*	53/40*		
				Average				40/34*	42/33*		

*Colorimetric/Microbiologic. x—Not performed.

CONCLUSIONS

1. Chloromycetin Palmitate Suspension was found to be a practical preparation for administration of Chloromycetin to children and to adults who may require a palatable liquid form of this drug.

2. Evidence of intolerance and toxic reactions was not observed in this series of patients.

3. In children, peak blood levels were observed four hours after receiving the drug and significant levels were maintained through the sixth to eighth hour. After the eighth hour, a gradual fall of the blood level curve was evident. Single doses of 75 mg. per kilogram gave significant levels twelve hours after administration; 100 mg. per kilogram gave significant levels between the twelfth and eighteenth hour period.

4. Adults seemed to reach significant levels rapidly, and attained higher levels than did infants on a milligram per weight basis.

5. Urinary excretion estimates indicate a 46 per cent excretion during the first twenty-four hours.

6. These studies indicate that satisfactory blood levels would be attained in children following 50 to 100 mg. Chloromycetin base per kilogram per day, divided into four or six doses throughout a twenty-four-hour period.

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MODE OF ACTION OF STREPTOMYCIN IN RELATION TO THE CHANGES IN SPINAL FLUID SUGAR IN TUBERCULOUS MENINGITIS

I. The Role of Streptomycin* as a Reducing Agent and the Specificity of the Shaffer-Hartmann Method for Determining "True Glucose" When This Antibiotic Is Used (in vitro Experiments)

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With the Technical Assistance of Mrs. Herma Wolf, Miss Marie Morton, and Mrs Ruth B. Gerstung

STREPTOMYCIN has the following structural formula (Fig. 1), casual inspection of which reveals a glucoselike component. Since 1948, there have been reports which would indicate that the rise in spinal fluid sugar, after intrathecal therapy with streptomycin in tuberculous meningitis, was not true glucose but secondary to the chemical action of streptomycin as a reducing agent.[1, 2] For example, the observations of Alvaro and Nicola[2] may be summarized as follows: (a) In the treatment of tuberculous meningitis with 0.03 Gm. intrathecally (I.T.) administered streptomycin daily, there was noted after ten days a slow rise of the spinal fluid sugar to normal. (b) After treatment was discontinued for a ten-day period, there was a slow fall in the cerebrospinal fluid (C.S.F.) sugar to values as low as obtained prior to therapy. (c) When streptomycin was given by the lumbar route (0.03 Gm. I.T. every day) in cases of spinal block, the lumbar spinal fluid sugar was found elevated, whereas that of the ventricles was still low. (d) It was also demonstrated that varying concentrations of streptomycin solutions would give "false values" for sugar by the Hagedorn-Jensen method. Blank runs of similar small amounts of streptomycin would equal 12 to 31 mg. per 100 ml. of glucose, depending on the lot and type of streptomycin used. It was concluded that the apparent rise in

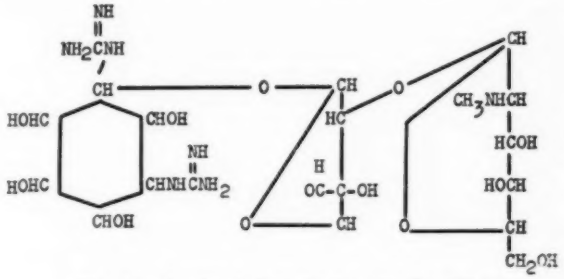

Fig. 1.—Structural formula for streptomycin.

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

*Streptomycin calcium chloride, Merck & Co., Inc.

**Work done while Senior Resident Physician at the St. Louis Children's Hospital.

the C.S.F. glucose in tuberculous meningitis was due to streptomycin or its breakdown products acting as glucoselike reducing substances rather than to true sugar.

To test their hypothesis, the following in vitro experiment was devised. All determinations were done by the Shaffer-Hartmann method as modified by Somogyi.[3]

In Part A, stock solutions of streptomycin in distilled water, ranging from 0.025 to 50 mg. per milliliter, were substituted as unknown solutions and run as "filtrate" without precipitation by copper sulfate and sodium tungstate. Stock solutions in 1:10 dilution were made to simulate conditions in the usual Shaffer-Hartmann procedure. Results are tabulated as "glucose equivalents" since streptomycin is not a true sugar.*

*Various concentrations of streptomycin in distilled water and in C.S.F. have been fermented by yeast.[4] Streptomycin is nonfermentable.

By examining the results (Table I and Fig. 2), it can be seen that there is a direct relationship between the concentration of streptomycin in the "filtrate" and "glucose equivalent." As noted in Table I, as little as 0.5 mg. per milliliter of streptomycin has a "glucose equivalent" of 13.8 mg. per 100 ml. if precipitation of the nonglucose reducing substance is not first effected with copper sulfate and sodium tungstate.

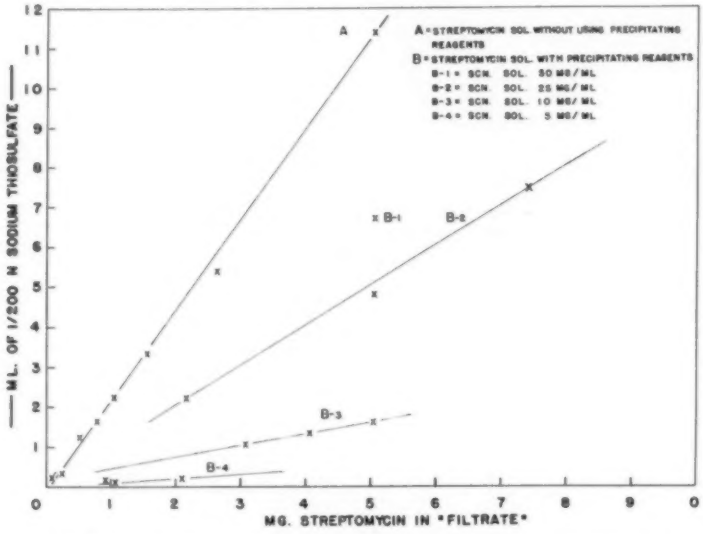
A = STREPTOMYCIN SOL. WITHOUT USING PRECIPITATING REAGENTS
B = STREPTOMYCIN SOL. WITH PRECIPITATING REAGENTS
B-1 = SCH. SOL. 50 MG./ML.
B-2 = SCH. SOL. 25 MG./ML.
B-3 = SCH. SOL. 10 MG./ML.
B-4 = SCH. SOL. 5 MG./ML.
A
B-1
B-2
B-3
B-4
ML. OF 1/200 N SODIUM THIOSULFATE
MG. STREPTOMYCIN IN "FILTRATE"
0 1 2 3 4 5 6 7 8 9 0
1 2 3 4 5 6 7 8 9 10 11 12

Fig. 2.—Titration of streptomycin solution with 1/200 N thiosulfate.

In Part B, stock solutions of comparable dilutions of the antibiotic were tested by the Shaffer-Hartmann method after addition of 5 per cent copper sulfate and 6 per cent sodium tungstate to precipitate nonglucose reducing substances from solution. It was found that the amount of streptomycin removed from solution depended on its concentration in the original stock solution. The results tabulated (Table II and Fig. 2) show that under 5 mg. per milliliter strep-

tomycin no longer gives a "glucose equivalent" by the Shaffer-Hartmann method. Table III compares identical stock solutions of streptomycin with and without precipitation by copper sulfate and sodium tungstate and illustrates the marked difference in "glucose equivalents" by the two methods.

Such results would indicate that streptomycin in the physiological range (below 0.5 mg. per milliliter to 1 mg. per milliliter) does not invalidate true glucose determination by

TABLE I. STREPTOMYCIN* SOLUTIONS TITRATED WITHOUT PRECIPITATING REAGENTS

STREPTOMYCIN STOCK SOLUTION (MG./ML.)	STREPTOMYCIN SOLUTION AS 1:10 FILTRATE (ML.)	STREPTOMYCIN DETERMINED (MG.)	1/200 N THIOSULFATE (ML.)	GLUCOSE EQUIVALENT OF ORIGINAL STOCK SOLUTION (MG./100 ML.)
50.0	1	5.0	11.39	1,323
25.0	1	2.5	5.36	644
10.0	1	1.0	2.24	278
5.0	3	1.5	3.22	131
2.5	3	0.75	1.61	66
1.0	5	0.50	1.22	32
0.50	5	0.25	0.47	14
0.25	5	0.125	0.23	8
0.10	5	0.05	0.13	0
0.05	5	0.025	0.10	0
0.025	5	0.0125	0.10	0

*Streptomycin Merck (calcium chloride complex), lot number 2141.

TABLE II. STREPTOMYCIN* SOLUTIONS TITRATED WITH THE PRECIPITATING REAGENTS

STREPTOMYCIN STOCK SOLUTION (MG./ML.)	STREPTOMYCIN SOLUTION AS 1:10 FILTRATE (ML.)	APPARENT STREPTOMYCIN DETERMINED (MG.)	1/200 N THIOSULFATE FOR TITRATION (ML.)	APPARENT GLUCOSE EQUIVALENT OF ORIGINAL STOCK SOLUTION (MG./100 ML.)
50	1	5.0	6.68	790
25	3	7.5	8.05	317
25	2	5.0	4.67	282
25	1	2.5	2.23	276
10	4	4.0	1.43	45
10	3	3.0	1.00	43
10	1	1.0	0.20	35
5	5	2.5	0.20	0
5	2	1.0	0.10	0

*Streptomycin Merck (calcium chloride complex), lot number 2141.

TABLE III. GLUCOSE EQUIVALENTS OF STREPTOMYCIN* WITH AND WITHOUT THE PRECIPITATING REAGENTS

STOCK SOLUTION STREPTOMYCIN (MG./ML.)	STREPTOMYCIN IN 1:10 FILTRATE (MG.)	GLUCOSE EQUIVALENTS (PART A) WITHOUT PRECIPITATING REAGENTS (MG./100 ML.)	GLUCOSE EQUIVALENTS (PART B) WITH PRECIPITATING REAGENTS (MG./100 ML.)
50.0	5.0	1,323.0	790.0
25.0	2.5	643.5	276.3
10.0	1.0	277.5	35.0
5.0	1.5	130.8	0
2.5	0.75	66.25	0

*Streptomycin Merck (calcium chloride complex), lot number 2141.

the Shaffer-Hartmann technique. Although our data were obtained with serial dilutions of the antibiotic in distilled water, similar results were noted in normal spinal fluid solutions.* We can conclude that the high "glucose equivalents" obtained by Alvaro and Nicola[2] were in part due to the Hagedorn-Jensen method of precipitating protein and other interfering substances. That method, therefore, would not seem reliable for determining true sugar in the presence of streptomycin.

SUMMARY

Streptomycin's chemical action as a reducing agent does not invalidate true glucose determinations (in vitro) by the Shaffer-Hartmann method when the concentrations of this antibiotic are within the physiological range.

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*When spinal fluid was incubated at 37° C. in combination with streptomycin 1 mg. per milliliter, some breakdown of the streptomycin molecule was noted at the end of ten days which amounted to 10 mg. per cent of nonglucose reducing substance. This would have very little effect in vivo, as streptomycin diffuses rapidly from the spinal fluid system (see Part II of this paper). Additional experiments in vivo were carried out with this in mind, and never could a nonglucose reducing substance attributable to intrathecal streptomycin be recovered from the spinal fluid. (See Part II of this paper.)

MODE OF ACTION OF STREPTOMYCIN IN RELATION TO THE CHANGES IN SPINAL FLUID SUGAR IN TUBERCULOUS MENINGITIS

II. Observations on the Effect of Intrathecal Streptomycin Treatment on the Cerebrospinal Fluid Sugar in Tuberculous Meningitis

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St. Louis, Mo.

With the Technical Assistance of Mrs. Herma Wolf, Miss Delores Minikis, Miss Marie Morton, and Mrs. Ruth B. Gerstung

SEVERAL observers have noted the rise in cerebrospinal fluid sugar after treatment with streptomycin in tuberculous meningitis.[1, 2, 3] In some instances they have reported that the spinal fluid sugar had little or no correlation with the apparent clinical course of the disease.[1, 2, 4] Different theories concerning this rise will be discussed in Part III. In this section we will note our findings without attempting to designate the mechanism involved.

Two groups of patients were observed quite closely after intrathecal streptomycin therapy for test periods of twelve to twenty-six hours. Blood and spinal fluid glucose and streptomycin levels were determined at frequent intervals during these periods, as indicated. The grouping of patients was designated as follows: Group A—patients who had no previous treatment with streptomycin, intrathecally; Group B—patients who had previous subcutaneous and intrathecal streptomycin.

Procedure.—Each C.S.F. (cerebrospinal fluid) sample was analyzed by the two methods outlined below:

Method 1—Shaffer-Hartmann technique as modified by Somogyi.[5]

Method 2—The following procedure was devised to determine "true glucose." A 1:10 dilution of spinal fluid was made in a volumetric flask, and aliquots were tested as below:

(a) 5 ml. were used as *filtrate* and the sugar content determined as above (Method 1).

(b) 5 ml. were fermented by yeast[6] and then treated as *filtrate* and sugar determined by Method 1. Therefore, a-b gave the value of "true" spinal fluid glucose. Since the precipitating reagents were not used in Method 2, this procedure gave a more accurate value for true sugar. As streptomycin is not fermented by yeast,[7] false values secondary to this antibiotic would have been apparent. The "true" sugar values differed only by ±6 mg. per 100 ml. from the results obtained by the Shaffer-Hartmann technique.

Group A. Patients Without Previous Treatment With I.T. Streptomycin

Two patients with tuberculous meningitis who had no previous therapy with intrathecal streptomycin were followed. All other medications were discontinued for a forty-eight-hour period. Oral feedings were given as indicated in Figs. 1, 2, and 3. The caloric value of the feedings was divided equally over a twenty-four-hour period.

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

*Work done while Senior Resident Physician at the St. Louis Children's Hospital.

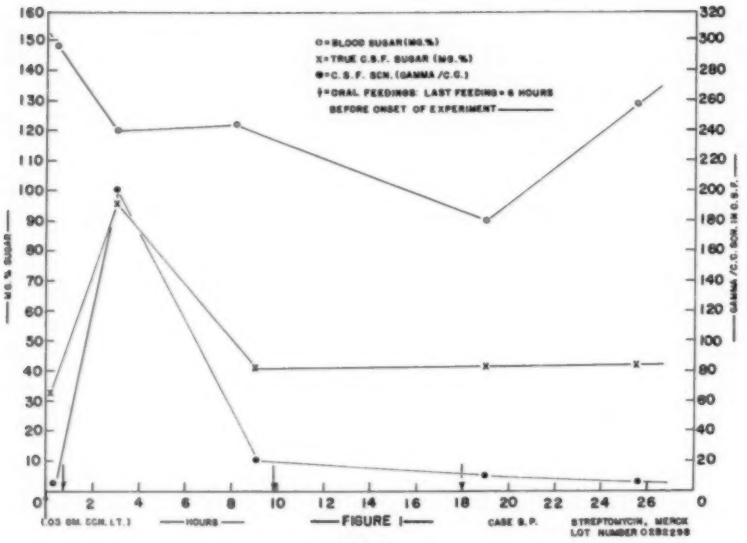
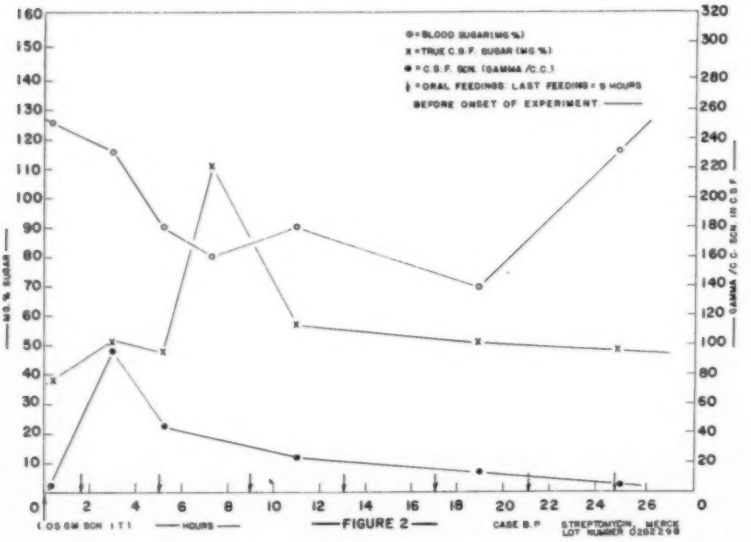

O = BLOOD SUGAR (MG. %)
X = TRUE C.S.F. SUGAR (MG. %)
● = C.S.F. SCN. (GAMMA / C.C.)
↓ = ORAL FEEDINGS: LAST FEEDING = 6 HOURS BEFORE ONSET OF EXPERIMENT
— MG. % SUGAR —
— GAMMA / C.C. SCN. IN C.S.F. —
— HOURS —
FIGURE 1
CASE B. P.
STREPTOMYCIN, MERCK LOT NUMBER 0282298

Fig. 1.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X = TRUE C.S.F. SUGAR (MG. %)
● = C.S.F. SCN. (GAMMA / C.C.)
↓ = ORAL FEEDINGS: LAST FEEDING = 6 HOURS BEFORE ONSET OF EXPERIMENT
— MG. % SUGAR —
— GAMMA / C.C. SCN. IN C.S.F. —
— HOURS —
FIGURE 2
CASE B. P.
STREPTOMYCIN, MERCK LOT NUMBER 0282298

Fig. 2.

CASE 1.—B. P., a 22-month-old white female, had proved tuberculous meningitis as revealed by physical findings, positive tuberculin, low C.S.F. sugar, increased C.S.F. protein, and acid-fast bacilli in the spinal fluid. Her meningitis was of two and one-half months' duration. At the time of the test period, the spinal fluid was markedly xanthochromic with a protein content of 416 mg. per 100 ml. Combined punctures with the instillation of indigo carmine into the ventricles was diagnostic of a spinal block. The Queckenstedt test showed almost no rise on jugular compression. A block was postulated by the neurosurgeons in the region of the fourth ventricle.

CASE 2.—D. L. was a 3-year-old white female who gave a history of contact with an aunt with massive pulmonary tuberculosis during the past year. Physical findings and spinal fluid chemical analyses were compatible with the diagnosis of tuberculous meningitis. She had a positive intradermal tuberculin test and evidence of right lower lobe tuberculous pneumonia and atelectasis. The duration of her meningitis, as well as could be ascertained from the history, was one month. Acid-fast bacilli were found in the spinal fluid.

Under the conditions outlined above, both patients were given 0.05 Gm. of streptomycin intrathecally between L-4 and L-5, after base-line chemical analyses were obtained. At frequent intervals the blood sugar, spinal fluid sugar, and streptomycin levels* were determined. Intrathecal streptomycin was administered a second time to patient B. P. forty-eight hours after the first instillation. Results on patients B. P. are graphed on Figs. 1 and

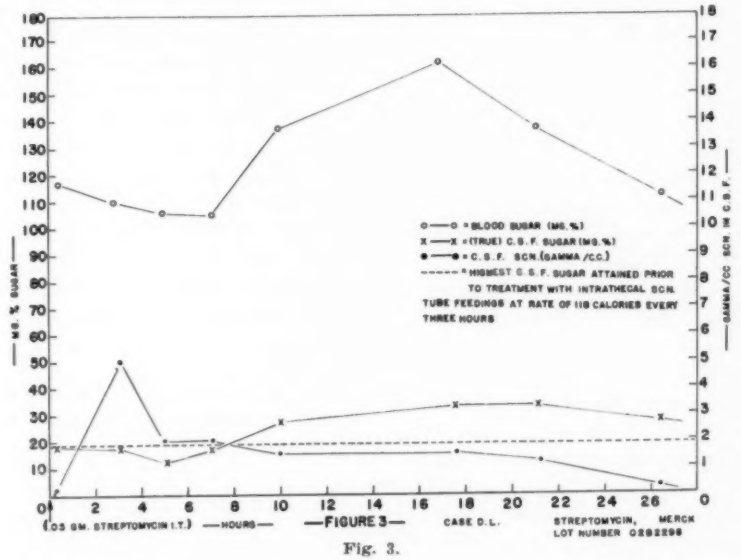
MG. % SUGAR
GAMMA/CC. IN C.S.F.
o—o = BLOOD SUGAR (MG.%)
x—x = (TRUE) C.S.F. SUGAR (MG.%)
•—• = C.S.F. SCN. (GAMMA/CC.)
------ = HIGHEST C.S.F. SUGAR ATTAINED PRIOR TO TREATMENT WITH INTRATHECAL SCN.
TUBE FEEDINGS AT RATE OF 110 CALORIES EVERY THREE HOURS
(.05 GM. STREPTOMYCIN I.T.) —HOURS—
—FIGURE 3—
CASE D.L.
STREPTOMYCIN, MERCK
LOT NUMBER 0282298

Fig. 3.

*Streptomycin levels were determined by bacteriological assay using serial dilutions of the unknown solution in nutrient broth adjusted to pH 7.6. The test organism used was an eighteen-hour growth of *E. coli* (strain isolated in our laboratory, No. 64-68) that was inhibited by 0.1 gamma per cubic centimeter of streptomycin and grew in 0.05 gamma per cubic centimeter of streptomycin. Sterility controls, growth controls, and streptomycin solutions of known concentrations were utilized in the procedure. In Figs. 1 through 5 and in the context of the paper, the C.S.F. streptomycin levels are given as the lowest figure in the range found by the above procedure: e.g., if the level is 200 to 400 gamma per cubic centimeter, 200 gamma per cubic centimeter is the figure used. The highest possible level is always double the figure given in the graphs and the context.

2. Results after intrathecal therapy on patient D. L. are graphed in Fig. 3.

Results.—After the first intrathecal streptomycin in patient B. P., there was a concomitant rise in the streptomycin level to 200 gamma per cubic centimeter and C.S.F. sugar to about 100 mg. per 100 ml. at the end of three hours (Fig. 1). Subsequently, the spinal fluid sugar fell to pretreatment levels of 38 mg. per 100 ml. at nine hours and remained at this level for the next sixteen hours. Streptomycin fell to 20 gamma per cubic centimeter at nine hours and then slowly to 5 gamma per cubic centimeter at the end of twenty-four hours. Fig. 2 is a graph of the second administration of 0.05 Gm. of streptomycin I.T. to patient B. P. On this occasion the rise in the streptomycin level to 100 gamma per cubic centimeter occurred at two hours, whereas the C.S.F. glucose did not rise until seven hours and then reached 105 mg. per 100 ml. After seven hours the C.S.F. sugar came down to pretreatment levels. Since the highest concentration of the antibiotic occurred five hours before the rise in spinal fluid sugar, this would offer further proof that its action as a reducing agent was not responsible for the rise in C.S.F. sugar. An analysis of the blood sugar findings in the case of B. P. reveals an initial fall of 30 to 45 mg. per 100 ml. when the spinal fluid sugar was rising to its peak. In Fig. 2 the blood sugar was 25 mg. per 100 ml. lower than the C.S.F. sugar at the time the spinal fluid sugar was at its maximum. This is not surprising since there is a lag of two to four hours between the blood and C.S.F. system in attaining an equilibrium.[8] At the end of twenty-four hours the blood sugar gradually rose to the same level as at the onset of the experiment.

The values of blood and spinal fluid sugar on patient D. L. are graphed in Fig. 3. In this subject the findings were in marked contrast to the previous patient. The spinal fluid glucose rose slowly from the seventh to the twenty-first hour, and the total increase was 14 mg. per 100 ml. (from 19 to 33 mg. per 100 ml.). The blood sugar values, too, were quite different. There was an initial drop of 14 mg. per 100 ml. lasting seven hours and then a rise that parallels the C.S.F. sugar to a peak of 160 mg. per 100 ml. (increase of 42 mg. in eighteen hours). The blood sugar then begins to fall until it reaches 115 mg. per cent at the end of twenty-five and one-half hours. The concentration of streptomycin at its maximum level in three hours was only 5 gamma per cubic centimeter.

GROUP B. C.S.F. SUGAR IN CHRONIC TUBERCULOUS MENINGITIS AFTER PROLONGED TREATMENT WITH INTRATHECAL AND PARENTERAL STREPTOMYCIN

The first two cases described, B. P. and D. L., did not have intrathecal streptomycin prior to the experimental period. They were rather vigorously controlled, in that no other medications were given during the test period.

However, because treatment of the patient has always been the major objective, we were not able in all instances to have such well-regulated experiments. The following data are presented with the supposition that other medications did not influence our results.

The three patients to be discussed had three to eight months of intensive treatment with parenteral dihydrostreptomycin, 1 Gm., and intrathecal streptomycin, 0.05 Gm. every day. The C.S.F. sugar was initially 10 to 18 mg. per 100 ml. and after four to eight weeks of treatment rose slowly to 25 to 30 to 45 mg. per 100 ml. Despite six to ten more months of treatment, all three children gradually became worse and developed considerable internal hydrocephalus.

The histories of the patients will be briefly reviewed.

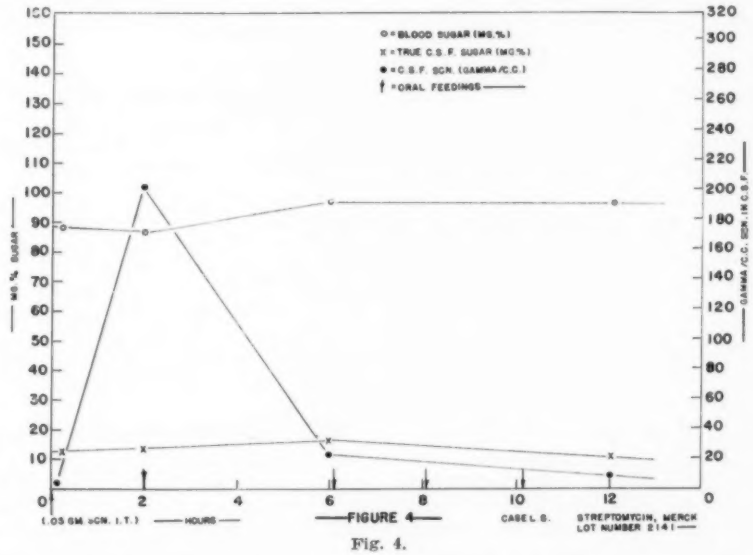
O = BLOOD SUGAR (MG. %)
X = TRUE C.S.F. SUGAR (MG %)
● = C.S.F. SCN. (GAMMA/C.C.)
† = ORAL FEEDINGS
MG % SUGAR
GAMMA/C.C. SCN. IN C.S.F.
HOURS
(.05 GM. SCN. I.T.)
CASE L. S.
STREPTOMYCIN, MERCK LOT NUMBER 214 (

FIGURE 4

Fig. 4.

CASE 3.—L. S. was first admitted to the St. Louis Children's Hospital on March 7, 1949, at 4 years of age. For the previous two and one-half years she had been followed in the outpatient clinic with an infiltration in her chest thought possibly to be pulmonary tuberculosis.

At the time of admission the tuberculin test was positive, and the C.S.F. sugar was 31 mg. per 100 ml. Other chemical analyses and C.S.F. cell counts were compatible with the diagnosis of tuberculous meningitis. Subsequently, acid-fast bacilli were found in the spinal fluid. Treatment consisted of 1 Gm. of dihydrostreptomycin intramuscularly daily for three months and two courses of intrathecal streptomycin from March 11 to April 8, 1949, and July 3 to Aug. 10, 1949. The C.S.F. sugar after four weeks of therapy averaged 40 to 50 Gm. per 100 ml.

She was followed as an outpatient until Dec. 27, 1949, when her illness became more severe, as indicated by temperature rise, headache, vomiting, and at that time she was readmitted to the hospital. From Jan. 2 to April 9, 1950, she received an additional sixty days of treatment with intra-

TABLE I

DATE	C.S.F. GLUCOSE MG. PER 100 ML.	PROTEIN MG. PER 100 ML.
12/27/49	7.0	114.5
12/29/49	7.0	112.0
1/ 4/50	7.0	118.3
1/ 6/50	11.7	

thecal streptomycin. The spinal fluid chemical analyses prior to the test period on Jan. 12, 1950, are shown in Table I.

In addition to intrathecal streptomycin treatment during this period, she also received intramuscular dihydrostreptomycin 0.25 Gm. b.i.d., Promizole 0.5 Gm. q.i.d., and para-aminosalicylic acid 2 Gm. t.i.d. On Jan. 12, 1950, twenty-four hours after previous intrathecal therapy, she received 0.05 Gm. of streptomycin intrathecally. C.S.F. streptomycin and sugar levels and blood sugar were followed at two, six, and twelve hours after I.T. streptomycin. These values are graphed on Fig. 4. There was no rise in the C.S.F. sugar above 10.7 mg. per 100 ml. during this interval.

The C.S.F. streptomycin concentration reached a peak of 200 gamma per cubic centimeter at two hours and then rapidly fell in six hours to 20 gamma per cubic centimeter and in twelve hours to 5 gamma per cubic centimeter.

After eight weeks of I.T. streptomycin therapy, her C.S.F. glucose rose to 30 mg. per 100 ml. Nevertheless, she expired on May 5, 1950. Autopsy findings revealed a tuberculoma in the hypothalamus near the optic tract. There was advanced internal hydrocephalus with slight lymphocytic infiltration in the spinal arachnoid tissue. The arachnoid over the cerebellum revealed marked fibrous thickening and lymphocytic infiltration.

CASE 4.—M. M., aged 2 years, was first admitted on Sept. 1, 1949, and discharged on May 6, 1950. The diagnosis of tuberculous meningitis was made by the criteria listed above. After hospital admission she received three months of intrathecal streptomycin (0.05 Gm. every day) and eight months of parenteral dihydrostreptomycin (1 Gm. every day). From Nov. 3 to Dec. 4, 1949, I.T. streptomycin was temporarily discontinued. From Dec. 5 to 12, 1949, 0.05 Gm. of streptomycin was given intrathecally twice a day. Table II is a record of the C.S.F. sugar and I.T. streptomycin therapy during this interval.

TABLE II

DATE	C.S.F. GLUCOSE (MG./100 ML.)	I.T. STREPTOMYCIN (GM.)
9/ 1/49 to 10/10/49	Averaged 18.0	0.05 Gm. every day
11/ 8/49	24.0	No I.T. streptomycin from
11/17/49	29.8	11/3/49 to 12/5/49
11/23/49	28.5	
11/30/49	34.5	
12/ 5/49 (9 P.M.)	----	0.05
12/ 6/49 (9 A.M.)	----	0.05
(4 P.M.)	93.5 (blood sugar 141 mg./100 ml.)	0.05
12/14/49	44.0	From 12/6/49 to 12/12/49
12/16/49	38.0	0.1 Gm. every day
1/ 1/50	50.0	From 12/14/49 to 1/1/50
1/ 1/50 to 5/6/50	Averaged 50.0	0.05 Gm. every other day

The data on M. M. show a gradual increase in C.S.F. sugar under treatment starting at eight weeks until relatively normal levels were reached (38 to 50 mg. per 100 ml.) at the end of twelve weeks. The most interesting feature, however, is the marked rise of C.S.F. sugar seven hours after I.T. streptomycin on Dec. 6, 1949. On this occasion, I.T. therapy was reinstituted after being discontinued for four weeks. The rise came after 0.1 Gm. of streptomycin was given in the nineteen-hour period. Prior to this, the C.S.F. sugar was never over 34 mg. per 100 ml. Now it reached 93.5 mg. with a blood sugar of 141 mg. per 100 ml. Unfortunately, no details are

known in this instance, but the trend seems to be comparable to those of D. L. and B. P., with an increase of C.S.F. sugar occurring after intrathecal therapy.

On Dec. 13, 1949, twenty-four hours after previous intrathecal therapy, base-line levels of streptomycin, blood, and C.S.F. sugar were obtained. Then 0.05 Gm. of streptomycin was given I.T. and the results of these values determined two, six, and twelve hours after treatment, as shown in Fig. 5. There was an increase in the C.S.F. sugar of 10 mg. per 100 ml. at six hours. At two hours the concentration of streptomycin reached 500 gamma per cubic centimeter.

On Jan. 11, 1950, pneumoencephalograms revealed communicating hydrocephalus.

CASE 5.—C. M., 8-year-old Negro male, was first hospitalized on March 30, 1951. At the time of admission he gave a one month's history of central nervous system disturbance. Positive tuberculin, spinal fluid chemical analyses, and physical findings were compatible with the diagnosis of tuberculous meningitis.

For the first five weeks of hospitalization, he received I.T. streptomycin 0.05 Gm. every day. Subsequently, I.T. therapy was given every other day until death twenty weeks after admission, on Aug. 12, 1951. He also had dihydrostreptomycin 1 Gm. every day (except from July 16 to 21, 1951) until one week prior to death. P.P.D.* was given during the last week of life in the lumbar region. Tibione, 40 mg. every day, was used in conjunction with the other antituberculous treatment.

The C.S.F. sugar levels are given in Table III.

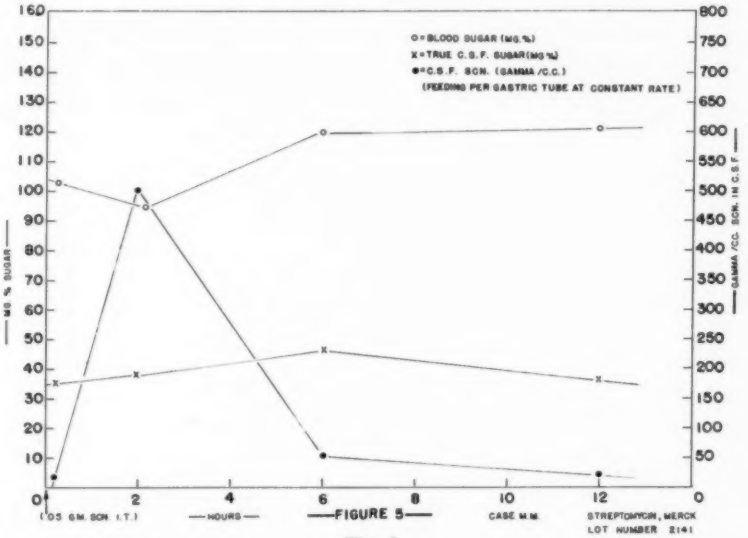

FIGURE 5

Fig. 5.

TABLE III

DATE	SUGAR (MG./100 ML.)	DATE	SUGAR (MG./100 ML.)
3/30/51	23.0	5/17/51	72.5
4/ 2/51	28.4	6/ 8/51	75.0
4/ 4/51	25.4	6/11/51	69.5
4/ 6/51	26.0	6/23/51	72.0
4/10/51	38.7	7/16/51	69.7
4/18/51	50.7	7/23/51	64.5
4/24/51	55.0	8/ 6/51	54.0
4/27/51	58.0	8/12/51	Expired
5/ 1/51	59.5		
5/ 4/51	67.0		

*Purified protein derivative—tuberculin—Lilly's.

After eighteen days of treatment the C.S.F. sugar increased to 50 mg. per cent and remained at a normal level until death. This patient again illustrates that an increase of cerebrospinal fluid sugar is not necessarily correlated with clinical improvement.

On July 16, 1951, after all parenteral and intrathecal streptomycin had been discontinued for twenty-four hours, 0.05 Gm. of streptomycin was given intrathecally. Blood and C.S.F. sugars were obtained as indicated in Fig. 6. As shown, there was very little change in the C.S.F. sugar nineteen hours after I.T. streptomycin.

In summary of cases L. S., M. M., and C. M., we note that all had three months or more of treatment with parenteral and intrathecal streptomycin. With the usual dose of 0.05 Gm. of streptomycin I.T., there was a rapid increase of C.S.F. streptomycin concentrations to 200 to 500 gamma per cubic centimeter (cases L. S., and M. M.) within two hours and then a rather rapid fall to 5 gamma per cubic centimeter in twelve to twenty hours. Two cases, L. S. and C. M.,

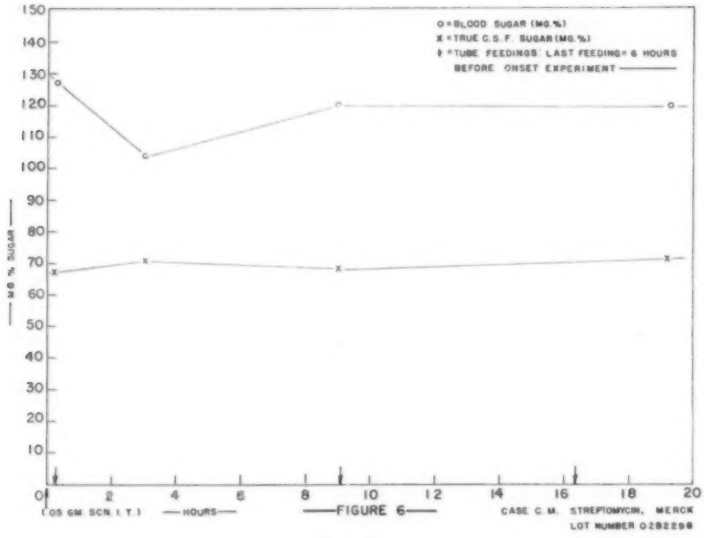
O = BLOOD SUGAR (MG.%)
X = TRUE C.S.F. SUGAR (MG.%)
= TUBE FEEDINGS: LAST FEEDING = 6 HOURS BEFORE ONSET EXPERIMENT
MG % SUGAR
HOURS
(.05 GM. SCR. I. T.)
FIGURE 6
CASE C. M. STREPTOMYCIN, MERCK LOT NUMBER 0282269

Fig. 6.

The course of the patient's illness was downhill. He developed an internal hydrocephalus, became comatose, and expired on Aug. 12, 1951. Autopsy findings revealed the following: caseo-calcified nodules in the right bronchopulmonary tree and in the tracheobronchial lymph nodes; caseo-calcified nodules were found in the spleen and liver. There was a chronic basilar meningitis and internal hydrocephalus.

showed very little variation in blood and C.S.F. sugars during the "test period." In the case of M. M., however, the streptomycin level reached a peak of 500 gamma per cubic centimeter at the end of two hours, and there was a rise in the C.S.F. sugar of 10 mg. per 100 ml. at the end of six hours. In addition, in case M. M., when streptomycin I.T. was discon-

tinued for one month and then 0.1 Gm. given in a twelve-hour period, seven hours after the last injection there was a rise of the C.S.F. sugar to 93.5 mg. per 100 ml. and a rise of blood sugar to 141 mg. per 100 ml. Prior to this injection, the C.S.F. sugar was never over 34 mg. and subsequently never over 50 mg. per 100 ml.

SUMMARY

1. Case histories and spinal fluid sugars are reviewed in five patients having tuberculous meningitis:

a. Case 1, B. P., had a block at the region of the fourth ventricle. This patient did not have previous I.T. streptomycin therapy.

b. Case 2, D. L., had a history of tuberculous meningitis of one month's duration. As in Case 1, there had been no prior treatment with streptomycin intrathecally.

c. Case 3, L. S.; Case 4, M. M.; and Case 5, C. M.—all had previous therapy with I.T. and parenteral streptomycin up to the test period.

2. In the two cases, B. P. and D. L., not having previous I.T. or parenteral streptomycin therapy, variable increases in the C.S.F. sugar were noted at intervals up to eighteen hours after treatment.

3. In Case M. M. after I.T. streptomycin had been discontinued for a four-week period and then larger amounts given (0.1 Gm. instead of 0.05 Gm.), there was a marked increase in the C.S.F. sugar.

4. In Case C. M. it was noted that there was a gradual rise in C.S.F. sugar eighteen days after I.T. and parenteral therapy were instituted. This did not correlate with clinical improvement because, as noted, the C.S.F. sugar remained elevated (within normal range) despite actual clinical deterioration and death.

5. In two cases, L. S. and C. M., after previous treatment with I.T. and subcutaneous streptomycin, there was very little rise noted in the C.S.F. sugar twelve to twenty-four hours after intrathecal streptomycin therapy.

In Case L. S., pretreatment levels of C.S.F. sugar and those during the test period were all near the low level of 10.7 mg. per 100 ml. In Case C. M., however, the levels prior to and during the test period were normal.

6. Evidence is presented that streptomycin's action as a nonglucose reducing substance is not responsible for the rise in spinal fluid sugar after intrathecal treatment with this antibiotic.

a. In Case B. P., the rise of C.S.F. sugar occurred five hours (Fig. 2) after the peak of streptomycin concentration in the C.S.F. This increase, being "true" sugar, would indicate that streptomycin's effect as a nonglucose reducing agent is not the cause of the increased spinal fluid sugar.

b. Increases in the C.S.F. glucose in Cases B. P., M. M., and D. L., during the test periods were demonstrated to have been due to "true" sugar.

CONCLUSIONS

1. Streptomycin intrathecally causes a rise in the C.S.F. sugar in the initial treatment of tuberculous meningitis.

2. This rise is not always correlated with clinical improvement in the disease process.

3. The increase in C.S.F. sugar is true glucose and is not due to streptomycin's action as a nonglucose reducing substance.

4. After treatment with streptomycin and further progression of the disease process, variable results in spinal fluid sugar are obtained after I.T. streptomycin.

We wish to thank Dr. J. Jaudon for use of data on his patient, C. M.

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MODE OF ACTION OF STREPTOMYCIN IN RELATION TO THE CHANGES IN SPINAL FLUID SUGAR IN TUBERCULOUS MENINGITIS

III. A Theory of the Mode of Action of Streptomycin in vivo With a Commentary on the Current Literature

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COMPREHENSIVE review of the physiology of the cerebrospinal fluid has been made by Katzenellenbogen[1] and others in regard to circulation, source, and constituents. One subject that has caused considerable debate is the etiology of the low sugar found in bacterial meningitis. Different observers have offered theories to account for the low C.S.F. sugar as follows:

(a) There is a decrease in the permeability of the blood-C.S.F. barrier to glucose.[2, 3]

(b) Damage to the meninges and choroid plexuses may increase the glycolytic rate of these tissues.[4]

(c) There is a consumption of C.S.F. glucose by the glycolytic activity of bacteria and cells. Recent work[5] would indicate that neither the cells nor the bacteria are the cause of the low C.S.F. sugar. We consider the paper of Ino[4] to be an important contribution in this field. He noted that the meninges and choroid plexuses of rabbits immediately post mortem were markedly glycolytic and assigned to these tissues the main role in the decreased C.S.F. glucose. Observations by one of us (R. F.) on meninges and choroid plexuses obtained at autopsy seem to confirm these data in man.

The disease entity with which we are concerned is tuberculous meningitis. Quite typically, the onset of this illness is characterized by low cerebrospinal fluid sugar (below 40 mg. per 100 ml.) in most of the cases.[6] After initial treatment with streptomycin, however, the spinal fluid sugar varies and may have very little bearing on the course of the disease. The purpose of this paper is to offer a theoretical explanation of the variability of spinal fluid sugar in tuberculous meningitis that is compatible with clinical-pathological findings and with laboratory data on the mode of action of streptomycin.

From a survey of clinical reports and our own observations, we have noted that the increase in cells found in the C.S.F. in this disease does not parallel the diminution in the sugar. The predominant cells are usually lymphocytes. It has been noted that the lymphocyte is not very glycolytic, having only one-fifth the glycolytic rate of the polynuclear leukocyte.[7] Second, it has been reported that the tubercle bacillus grows slowly with a low rate of glucose consumption.[8] We can, therefore, dismiss these two elements in further discussions of changes in spinal fluid sugar in tuberculous meningitis.

Clinicians are in agreement on the initial rise in C.S.F. sugar[9, 10, 11] after intramuscular or intrathecal strepto-

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mycin treatment. This rise usually occurs in two to eight weeks but on several occasions was noted two to four days after institution of therapy. Prior to treatment with this antibiotic, it was characteristic of the C.S.F. sugar in tuberculous meningitis to approach zero, and death ensued in a rather short time.[6] Further clinical observations after prolonged streptomycin treatment reveal values of spinal fluid sugar that have been difficult to correlate with the course of the disease. For example, Levinson[6] found that nine out of twelve cases in relapse had normal sugars. Lincoln and Kirmse[9] states that two patients previously treated with streptomycin for miliary tuberculosis had normal sugars when the diagnosis of the meningitis was made.

In the past, the initial rise of the spinal fluid after treatment had been attributed to two factors: (1) improvement in the course of the illness and (2) streptomycin's property as a nonglucose reducing agent.[12, 13] Our data given in Parts I and II tend to refute both of these hypotheses.

COMMENTARY ON THE LITERATURE

There is an increasing literature on the inhibition of cellular and bacterial carbohydrate metabolism by streptomycin. Since the results are pertinent to our hypothesis, they will be summarized.

(a) Henry and associates[14] have shown that streptomycin in concentrations just bacteriostatic noncompetitively inhibits the metabolites of certain carbohydrate intermediates in susceptible strains of *Staphylococcus aureus, Bacillus cereus,* and *Shigella sonnei.* Resistant strains of these organisms were not at all affected by high concentrations of streptomycin. In another report, Henry and coworkers[15] state that with *Shigella sonnei* coincident with inhibition of multiplication by streptomycin there was an inhibition of carbohydrate substrate utilization and inhibition of oxygen consumption by the cell.

(b) One of us[16] has substantiated the above in a dependent strain of *Staph. aureus.* Streptomycin (under conditions of the experiment) inhibited the glycolysis of glucose in concentration of 1 mg. per cubic centimeter.

(c) Oginsky and associates[17] have worked with streptomycin-sensitive *E. coli.* They concluded that in susceptible strains streptomycin specifically inhibits the oxaloacetic-pyruvate condensation.

(d) The work of Umbreit and Tonhazy[18] with liver, kidney, and brain homogenates subjected to mild injury, such as heat, showed that streptomycin would inhibit the oxaloacetic-pyruvate condensation in concentrations as low as 50 to 60 gamma per cubic centimeter. They conclude, however, that in the intact animal permeability factors apparently prevent streptomycin from acting at the site of this reaction. They believe these permeability barriers apparently exist not only at the cell wall but also in the mitochondria and may be chemical as well as physical in nature. When the barriers are overcome, however, streptomycin does inhibit this key reaction of carbohydrate metabolism.

(e) Lastly, Harpier and Quastel[19] have noted that in acetone extracts of beef brain n-acetylglucosamine inhibits the phosphorylation of glucose, fructose, and d-glucosamine. Since

the n-acetyl-1 glucosamine unit is in the streptomycin molecule, this might further support the evidence that streptomycin inhibits carbohydrate metabolism of the cell and certain bacteria.

In presenting our theory on the mode of action of streptomycin on C.S.F. sugar in tuberculous meningitis, we fully realize the risk involved in drawing conclusions from a limited clinical study. However, the concept is new, and if only to stimulate further investigation in this field, it will be presented in detail.

On the basis of our clinical and laboratory data (Parts I and II), we postulated the following mechanism to explain the C.S.F. sugar changes under streptomycin therapy. Normally, in the intact cell, chemical and physical structure is of such a nature that streptomycin does not interfere with its metabolic processes. However, in tuberculous meningitis, it may be hypothesized; there is a cellular change in the meninges, secondary to inflammation, and sugar is oxidized at an increased rate by the diseased tissue, accounting for the characteristically low sugar. Under streptomycin treatment, the carbohydrate metabolism of the cell is inhibited, and the sugar is no longer utilized. Subsequently, there is an increase in spinal fluid sugar. What this may mean is simply a decreased utilization by the tissues as long as streptomycin is present in concentration sufficient to inhibit the reaction. If the flow of spinal fluid is unimpaired, the sugar continues to flow into the spinal system until an equilibrium is reached.

The increased diffusion of streptomycin in inflammation of the meninges would explain the early rise in sugar with intramuscular as well as intrathecal therapy. Thus, in Lincoln's[9] two patients undergoing streptomycin therapy for miliary tuberculosis, the normal sugar values with the onset of tuberculous meningitis would be plausible. Levinson's[6] findings of normal spinal fluid sugars in nine out of eleven cases in relapse are not surprising if the meninges are no longer glycolyte.

Variations in diffusion of streptomycin and spinal fluid sugar, secondary to exudate formation, length of the disease, previous therapy with streptomycin, and length of time from streptomycin administration, might all be important factors. On this basis we could account for the variable sugar findings in the chronic stage of the disease and the rather rapid increase in the acute stage if there is no impediment to spinal fluid flow and streptomycin diffusion.

No doubt the glycolysis of the C.S.F. sugar is based on enzyme systems which catalyze the reaction. According to Dixon,[20] the Michaelis equation is fairly constant in most enzymatic processes: $v = \frac{kES}{Km + S}$. In this equation, E is the amount of enzyme; k represents its catalytic activity; S is the substrate concentration; Km is the reciprocal of the affinity; and v equals the velocity of the reaction.

We can substitute in this equation to illustrate the variables involved in the glycolysis of carbohydrate by the meninges and choroid plexuses in tuberculous meningitis:

v = velocity or rate of glycolysis,

E = the cellular enzyme responsible for the glycolysis.

Its concentration is dependent on:

(a) Area of tissue involved in acute inflammation, area of inflamed tissue in contact with streptomycin.

(b) Concentration of enzyme inhibitor (streptomycin) in the C.S.F.

(c) Degree of cellular destruction. Fibrous tissue would contain little enzymatic or glycolytic activity, but the acutely inflamed tissue would possess this property.

S = substrate concentration or the concentration of glucose in the C.S.F. This would be *inversely related* to the concentration of the cellular enzyme. For example, if there is a large amount of enzyme, the concentration of glucose will be small, and, conversely, with small quantities of enzyme the over-all glucose concentration will be increased. The substrate concentration would be *directly related* to the amount of enzyme inhibitor, streptomycin. Lastly, the C.S.F. sugar would be subject to a third variable—the permeability of the blood-C.S.F. barrier and free flow of C.S.F.

In Cases B. P. and D. L. reviewed in Part II, the situation might be diagrammed as in Fig. 1. The curves represent the type of elevation in C.S.F. sugar which was obtained in each instance.

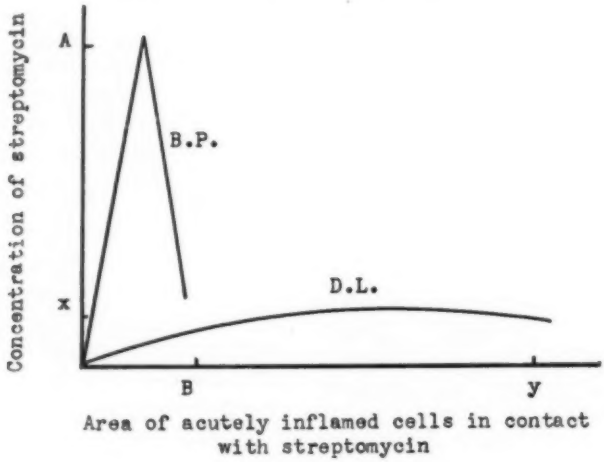

Fig. 1.

Case 1, B. P., probably had a cisternal block and would be illustrated on this graph by points *A* and *B*. In this instance the concentration of streptomycin was high because of the reduced volume of spinal fluid into which streptomycin was injected. The area of inflamed cells exposed to the antibiotic was comparatively small. Subsequently, as the enzymatic inhibitor (streptomycin) is increased and the cellular area (amount of the enzyme) decreased, the inhibition of glycolysis is marked. Thus we get high concentrations of sugar for a short period of time until the streptomycin diffuses from the subarachnoid space, and carbohydrate metabolism is no longer inhibited.

In Case 2, D. L., the concentration of streptomycin is at a lower level (5 to 10 gamma per cubic centimeter at its peak in three hours); the area of inflamed tissue exposed to streptomycin is greater as no spinal block is present (points x and y). As can be expected, the inhibition of cellular

glycolysis is slower (smaller concentration of enzyme inhibitor) and more prolonged (greater cellular area or enzyme involved), and the glucose rise is steady but not as high, taking twenty-one hours to reach its peak.

Lastly, a comment in regard to the blood sugar findings in these cases. The elevation in the C.S.F. sugar preceded or paralleled varying degrees of rise in the blood sugar. In no instance did the increase in blood sugar precede that of spinal fluid sugar. This would negate the conclusion that increase in C.S.F. sugar was secondary to a rise in blood sugar caused by intrathecal streptomycin.

In Part II, three patients who had had treatment with intrathecal streptomycin were described. These cases, L. S., M. M., C. M., all had three months or more of treatment before the "test periods." All of these patients had x-ray and/or autopsy evidence of communicating hydrocephalus. This would imply that the free flow of spinal fluid was prevented over the surface of the brain. Since four-fifths of the C.S.F. is supposedly absorbed by the arachnoid villi, poor absorption would account for the high streptomycin levels two hours after the intrathecal injection in these cases. The failure of a significant rise (L. S. and C. M.) in C.S.F. sugar during the experimental periods might be explained as follows.

(a) All of these patients had previous intrathecal and parenteral streptomycin treatment. It might be postulated that the inhibition of cellular carbohydrate metabolism was at its maximum with the concentration of streptomycin attained and that an equilibrium had been reached between the blood and C.S.F. sugar.

(b) The chronically inflamed cells of the meninges were no longer glycolytic and could not be affected by streptomycin. In support of the latter are autopsy reports[21] of fibroplastic reaction in the meninges in chronic tuberculous meningitis treated with streptomycin.

(c) Poor exchange between blood-C.S.F. systems.

However, when the amount of streptomycin was doubled in M. M., there was a marked increase in C.S.F. (and blood) sugar. Thus with higher quantities of streptomycin, it might be assumed there was still evidence of inhibition of cellular carbohydrate metabolism in this patient.

ANALYSIS OF THE MATERIAL

Finally, a word concerning interpretation of the results. Two objections to the material in this paper are suggested.

(a) Is the finding of increased C.S.F. sugar secondary to I.T. streptomycin due to a "foreign body" reaction? We think this is unlikely. Mader,[1] for example, introduced foreign substances—Ringer's solution, air, serum—and observed within thirty to sixty minutes a steep rise of blood sugar up to 100 mg. per 100 ml. and more above the original level. In some cases, the simultaneous determination of C.S.F. dextrose showed a certain parallel but delayed increase. Other workers[1] have not always found an increase in C.S.F. sugar in intraspinous serum therapy. Examination of Figs. 1, 2, and 3 in Part II, after intrathecal streptomycin, reveals an immediate decrease in the blood sugar when the C.S.F. sugar was reaching its peak. In three to four hours there follows a rise of varying degrees in

these cases. This is exactly opposite to the correlation of blood and C.S.F. sugar in the instances described by Mader.

(b) The experiments were not done under fasting conditions. Wherever indicated by arrows (Part II), the oral feedings were of equal number of calories in the individual case. Tube feedings were at a constant rate over a twenty-four-hour period. With the concomitant determinations of blood and C.S.F. sugar[22] under these circumstances, the above objection seems of little importance.

SUMMARY

A theory on the mode of action of streptomycin in tuberculous meningitis is presented that explains the rise of C.S.F. sugar after treatment with streptomycin. The hypothesis is formulated to correlate known clinical observations and laboratory data: Streptomycin in the injured cell in tuberculous meningitis causes inhibition of carbohydrate metabolism. The increase in spinal fluid sugar noted after the initial treatment with streptomycin is secondary to decreased utilization of glucose by the living cell and unimpaired flow of spinal fluid.

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TERRAMYCIN BY SUBCUTANEOUS CLYSIS

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TERRAMYCIN by clysis is a useful and previously unreported mode of parenteral broad-spectrum antibiotic therapy. The discovery and development of aureomycin, chloramphenicol, and terramycin have offered to the physician additional antiinfectious agents of wide range, high potency, and low order of toxicity. They can be conveniently administered by mouth as they are well absorbed through the intestinal tract. In addition, preparations of terramycin and aureomycin are commercially available for intravenous use. Their general usefulness, however, has been somewhat curtailed for want of a more easily administered form for parenteral use.

In the management of many sick infants and children, oral medication may not be feasible, frequently unwise, and sometimes, as in the surgical patient, contraindicated. In the event that administration by vein is technically difficult, as it occasionally is even in the best of hands, or in the event that adequate personnel or equipment is not readily available, the physician is faced with practical difficulties in the proper care of his patient. He may be forced to turn to other therapeutic agents such as penicillin and streptomycin which can be given intramuscularly, even though the broad-spectrum antibiotic has been shown to be the drug of choice either by clinical response or by appropriate bacterial sensitivity testing. The more frequent occurrence of bacterial strains resistant to penicillin or streptomycin as well as patient hypersensitivity to penicillin may pose additional problems; thus the ultimate therapy may fall short of the optimal.

This report describing the use of terramycin by the subcutaneous route is presented primarily as a practical aid to the practicing physician when such situations arise. Likewise parenteral terramycin when indicated can accompany the initial clysis so frequently given in any acute febrile illness requiring fluid replacement, or can more successfully form the initial phase of treatment until oral medication is begun. Hypodermoclysis has been one of the most widely used and safest methods for the restoration of water and electrolytes. With the proper attention to the necessary safeguards and a recognition of its limitations, the procedure can be conveniently and satisfactorily carried out by members of the nursing staff. The use of terramycin in this fashion has proved to be a very worth-while therapeutic adjunct on our infant's and children's services.

MATERIALS AND METHODS

The pertinent clinical and physical properties of terramycin were examined. Briefly, terramycin is an antibiotic substance extracted and crystallized from the fermentation products of a mold.[1] As an amphoteric substance it will form an alkaline or acid

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salt.[2] In the amphoteric form it has a pH of about 5 with limited solubility in aqueous solution and as such has been effectively utilized in a pleasant tasting suspension for oral administration. This parent form or terramycin base, as it is sometimes called, has similar antimicrobial activity and comparable intestinal absorption characteristics[3] to the more widely used hydrochloride salt found in the capsules, topical ointment, and intravenous preparations. The more soluble terramycin hydrochloride in aqueous solution has a pH of 1.5 to 2.0 and necessitates the addition of a chemical buffering system to bring such a solution near neutrality for intravenous use.[4] This is satisfactorily accomplished by the addition of the sodium salt of a simple amino acid, glycine, which produces a relatively stable solution with a pH of about 9. It is this formulation of terramycin that is used by hypodermoclysis throughout this study.

In preparation for therapeutic trial, a group of children were given terramycin by clysis in increasing concentrations and in various single doses to determine the degree of local tolerance and the level of the antibiotic obtained in the blood serum. These children were free of renal or cardiac disease. The patients included in the clinical study were routine admissions to the ward and private pediatric service of the St. Michael's Hospital. Serum and cerebrospinal fluid levels were performed by a modification of a twofold dilution turbidimetric technique previously described by Rammelkamp[5] using a *Streptococcus pyogenes* as the test organism with a minimal inhibitory concentration for terramycin of 0.156 μg per cubic centimeter. Venous blood serum samples were frozen after separation until bioassayed.

Terramycin assays to determine the compatability of terramycin in hyaluronidase solution, however, were performed by a rapid turbidimetric method devised by Kersey[6]; *Klebsiella pneumoniae* is employed as the test organism and values obtained photometrically are taken off a standard curve. The hyaluronidase used in this portion of the study was Wydase. This and other commercially available brands of this enzyme, however, were used in the patient.

RESULTS

Our experience with terramycin by the intravenous route has been good. It has been effectively used without difficulty by continuous drip infusion for several days in the smallest infant, a less than 1 mg. per cubic centimeter dilution usually being employed with the aid of a polyethylene tube following "cut-down" or other techniques. It was therefore felt that it might also be worth while to investigate the possibility of employing intravenous terramycin by subcutaneous clysis. A review of previous animal study[7] disclosed that large volumes of terramycin in the buffered intravenous form have been given in concentrations up to 10 mg. per cubic centimeter of water or physiological saline by subcutaneous injection with little or no apparent discomfort or gross evidence of local tissue reaction upon post-mortem examination. These data supported the impression that a trial in infants and children was warranted.

Initial Administration in Children.—Several infants were initially given small amounts of a ¼ to ½ mg. per

cubic centimeter solution subcutaneously without apparent discomfort or local irritation. Subsequently, these and other infants were given larger volumes by drip clysis in concentrations up to 5 mg. per cubic centimeter of saline without untoward reaction beyond an occasional mild erythema and induration, not unlike that which one may sometimes observe following clysis of 5 per cent dextrose or protein hydrolysate solutions; several were given repeated clysis with equally encouraging results. Darrow's, 1/6 M sodium lactate, or 2½ per cent dextrose solution when employed as a diluent in place of physiological saline, was equally as well tolerated. Terramycin is stable and chemically compatable in these solutions and they can be successfully used when indicated. Hyaluronidase was frequently added to facilitate absorption; however, good local tolerance was noted with or without this enzyme. Protein hydrolysate or Ringer's solution was not used as it was noted that a turbid solution or a fine precipitate sometimes formed following the addition of terramycin.

As concentrations of 1 to 5 mg. per cubic centimeter easily offered adequate opportunity for full therapeutic dosage of terramycin in the usual clysis volume, it was decided that it was unwise and unnecessary to attempt to utilize higher concentrations in this manner.

Biological Campatability With Hyaluronidase.—Since hyaluronidase is not uncommonly employed in hypodermoclyses as a spreading factor to enhance absorption and since it was added to many of the initial clyses, biological assays to detect any inactivation of terramycin solutions by the enzyme were performed. Mixtures were similar to those we used in the patient, namely, one turbidity reducing unit, or its equivalent, to 1 c.c. of 1 and 5 mg. per cubic centimeter of terramycin solution. The aqueous solutions were tested at temperatures of 5° C. and 25° C. over a period of twenty-four hours. No loss of potency of terramycin in the presence of hyaluronidase was noted as shown in Table I. One milligram of terramycin hydrochloride equals approximately 925 units of activity; however, 1 mg. of anhydrous terramycin amphoteric as a standard is assigned a value of 1,000 units. These assay figures represent comparable values within the degree of error of the method.

TABLE I. THE STABILITY OF TERRAMYCIN WITH HYALURONIDASE

SOLUTIONS	TEMPERATURE	UNITS OF ACTIVITY/ML. AT HOURS			
		0	1	6	24
Solution 1:					
1 mg. terramycin hydrochloride with	5° C.	890	945	930	1,070
1 T. R. unit hyaluronidase per ml.	25° C.	890	1,040	885	1,430*
Solution 2:					
5 mg. terramycin hydrochloride with	5° C.	4,800	5,080*	4,700	4,840
1 T. R. unit hyaluronidase per ml.	25° C.	4,800	3,660*	4,940	4,660

*These figures lay somewhat outside the usual assay variation.

Absorption and Blood Serum Levels.—In order to more clearly define a

terramycin dosage regimen by this type of administration and to be assured of its delivery into the blood stream in adequate concentration from the subcutaneous site of injection, terramycin blood serum determinations were done. Venous blood samples were drawn at suitable intervals following single doses of from 10 to 25 mg. per kilogram body weight. Hyaluronidase was used throughout in these patients. Both gravity-drip and "push-in" clyses were employed as indicated, with a terramycin solution of from 1 to 5 mg. per cubic centimeter concentration. By the gravity method, administration was complete within one hour. These data are summarized in Table II.

Table II. Terramycin Serum Levels Following Single Clyses

Patient	Age (mo.)	Weight (kg.)	Dosage/body weight (mg./kg.)	Serum concentration μg/c.c., at hours			C.S.F. concentration μg/c.c., at hours	
				1	4	12	1	12
T. F.	6	8.0	25	20	20	2.5		
G. M.	10	10.6	25	5	5	2.5		
B. M.	6	7.2	20	10	5	2.5		
E. S.	1½	4.2	12.5	5	5	2.5	None detected*	None
S. C.	1	3.6	12.5	5	5	1.25		
J. Ke.	1	4.0	10	5	5	2.5	None detected	
B. F.	12	10.0	10	2.5	1.25	0.625		
P. B.	2	5.1	10	2.5	2.5	1.25		
J. K.	6	6.8	10	2.5	1.25	0.625		

*Less than 0.15 μg per cubic centimeter.

In two patients (B. M. and J. K.), without apparent meningeal inflammation, lumbar puncture and cerebrospinal fluid assay revealed no demonstrable terramycin in spite of good serum values. These cerebrospinal fluid samples, taken simultaneously with the serum samples, are included in Table II.

Clinical Experience.—To confirm the therapeutic efficacy as well as the safety of this untried mode of administration, terramycin by clysis was employed a total of 254 times in the management of thirty-six patients on the ward and private pediatric service of St. Michael's Hospital with excellent results. Following initial therapy with terramycin by clysis, most of these children were given oral terramycin at a dosage of 25 to 50 mg. per kilogram body weight per day; a concentrated drop form was used in young infants and a raspberry-flavored suspension in older infants and children. Clinical response was usually evident before clysis therapy was discontinued; other chemotherapeutic agents were also used, usually prior to admission or in a few when the response seemed slow. Specific bacteriological data were not obtainable in most patients; a mixed flora or no predominating organism was usually found. A diagnosis of bronchopneumonia was supported by x-ray. All clysis were tolerated well, and no local or systemic untoward reactions were observed.

Table III includes all cases in which terramycin by clysis was used. A dose of terramycin of 10 mg. per kilogram body weight every twelve hours in a 1 mg. per cubic centimeter concentration was routinely employed in most of these children.

TABLE III. SUMMARY OF CHILDREN TREATED WITH TERRAMYCIN CLYSES

PATIENT	AGE (MO.)	DIAGNOSIS	NUMBER OF CLYSES	OTHER THERAPY*	CLINICAL RESULTS
P. F.	4	Bronchopneumonia Otitis media	8	TM, P	Excellent
M. N.	15	Bronchopneumonia	12		Excellent
J. S.	30	Bronchopneumonia	5	TM	Good
C. J.	10	Bronchopneumonia Congenital heart disease	7	TM	Good
G. S.	4	Bronchopneumonia Mongolism	14	P & S aerosol	Excellent
J. Z.	2	Bronchopneumonia Eczema	16	TM I.V., SD, P	Slow response
W. W.	7	Bronchopneumonia with pleural effusion	6	TM, P	Good
R. C.	13	Bronchopneumonia	6	P & S aerosol	Good
E. S.	1	Congenital cyst of lung Empyema	18	P	Infection responded Operative death
B. G.	½	Aspiration pneumonia Prematurity	6		Good
P. T.	6	Bronchiolitis Congenital heart disease	2	P, S	Poor
D. G.	21	Bronchiolitis	8	TM	Good
C. P.	1	Bronchiolitis Congenital heart disease	6	P	Poor
B. R.	1	Bronchiolitis Prematurity	4	TM, P	Satisfactory
M. G.	7	Bronchiolitis Otitis media	13	TM, P, SD	Fair
D. F.	6	Bronchiolitis	12	TM, TM aerosol	Excellent
N. F.	4	Bronchiolitis	1	TM, TM aerosol	Excellent
A. B.	6	Bronchiolitis	6	TM aerosol	Good
M. B.	13	Bronchiolitis	4	TM	Good
D. R.	12	Bronchiolitis	6		Good
S. B.	6	Tonsillitis	6		Excellent
H. D.	9	Tonsillitis Otitis media enteritis	18	TM I.V., TM	Good
M. M.	12	Tonsilitis	9		Good
J. S.	5	Otitis media	1	TM	Good
P. T.	12	Otitis media	2	P, SD	Slow response
B. D.	3 da.	Otitis media Prematurity	8	P, SD	Slow response
M. G.	1	Enteritis	6	TM I.V., P	Satisfactory
J. D.	18	Enteritis	4		Satisfactory
P. S.	5	Enteritis	6	SD	Slow response
P. B.	2	Enteritis	6		Good
A. L.	14	Gastroenteritis	6		Good
B. P.	4 da.	Clinical sepsis	6		Good
D. W.	20	Penetrating wound, abdomen	4		Good
M. S.	48	Cellulitis, scalp Hydrocephalus	4	TM	Good
T. W.	6	Roseola infantum	6		Course unchanged
P. D.	10	Roseola infantum	2		Course unchanged

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*TM, terramycin; P, penicillin; S, streptomycin; SD, sulfadiazine.

DISCUSSION

From the foregoing information it is evident that the use of a terramycin solution with a concentration of 1 mg. per cubic centimeter enables one to give an adequate dose of this antibiotic by hypodermoclysis with a wide margin of local toleration and safety. Concentrations above 5 mg. per cubic centimeter were not used and are not recommended. As demonstrated in the blood absorption curves, a dose of 10 to 25 mg. per kilogram (4.5 to 11.4 mg. per pound) body weight, provides a serum level above the concentration necessary to inhibit most bacterial pathogens.

Hobby and Welch and their coworkers in jointly examining their data on the activity of terramycin against 109 strains of a large variety of gram-positive and gram-negative bacteria[8] found that 56 per cent were sensitive to concentrations of less than 1.0 μg per cubic centimeter and 83 per cent to less than 5.0 μg per cubic centimeter. The organisms causing the more commonly encountered illnesses are fortunately among the most sensitive. The possibility of wide strain variability among each specie of course must be recognized. Significant serum levels are also found at twelve hours by this route of administration indicating that a twelve-hour schedule would be permissible.

Although one must be cautious in attempting to correlate blood serum levels or in vitro data with clinical application too closely, they nevertheless aid one in establishing a rational therapeutic regimen. Tissue concentration as well as immunological and cellular body defense mechanisms are also operative in the patient and must be given proper clinical consideration.

Hunt and colleagues[9] have recently reported in detail the results of their studies on the absorption and distribution of terramycin and have thus furnished needed information concerning this important antibiotic in chil-

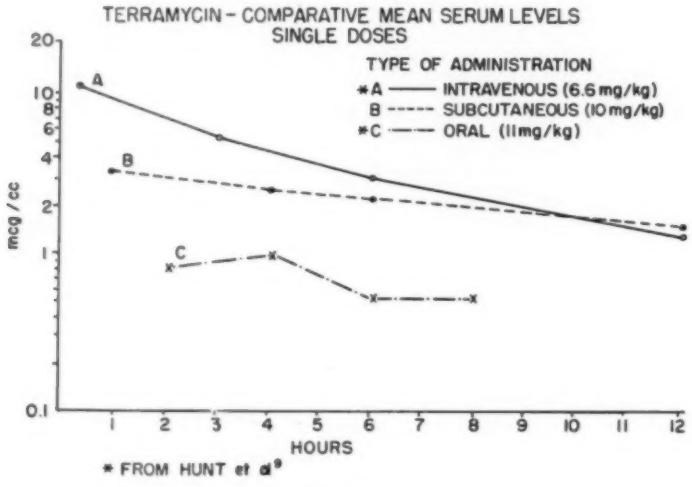

Chart I.

dren. As one would suspect, terramycin serum levels obtained by subcutaneous administration lay intermediate between the values obtained by these investigators following the oral and intravenous routes. This can be better visualized by a composite graph, as in Chart I, using comparable dosages by these modes of administration.

Our findings support those of others,[9, 10, 11] that the diffusion of terramycin into the cerebrospinal fluid through the normal meninges is poor, although levels up to one-fourth of that of the blood serum were detected by Hunt and associates in normal children. Pulaski and co-workers[12] have emphasized that the permeability of the meninges is altered and the diffusion of terramycin into the spinal fluid is enhanced in the presence of meningeal disease; they found an adequate concentration of 3.84 μg per milliliter in an adult patient receiving terramycin intravenously. Hoyne and Riff[13] have reported on the effective use of terramycin in meningitis.

A simplified table for ready reference in the use of terramycin by hypodermoclysis in various age groups may be formulated employing a terramycin concentration of 1 mg. per cubic centimeter, a twelve-hour dosage of 10 mg. per kilogram (or approximately 5 mg. per pound) body weight and a reasonable fluid volume of 10 c.c. per kilogram (or approximately 5 c.c. per pound) body weight, as in Table IV.

An occasion for using clysis therapy in older children or adults does not frequently arise but it may be of great advantage in the obese or seriously ill patient when parenteral terramycin is needed and accessible veins have been exhausted.

SUMMARY AND CONCLUSIONS

The need for an easily injectable broad-spectrum antibiotic is recognized. The readily available intravenous form of terramycin employed as a subcutaneous clysis meets this need in the infant or child patient. Successful preliminary trial and extensive clinical use has demonstrated its safety and efficacy. The satisfactory response obtained in a variety of common infections is reported. Terramycin serum levels were performed following various single doses to confirm its rapid entrance into the blood stream and to aid in establishing a proper dosage regimen. Data demonstrating the biological compatability of this antibiotic with hyaluronidase are included. Terramycin may be added to physiological saline, dilute dextrose solution, or to 1/6 M sodium lactate and Darrow's solutions when they are needed for electrolyte repair. Suggested dosage

TABLE IV. SUGGESTED DOSAGE SCHEDULES FOR TERRAMYCIN BY CLYSIS TWELVE-HOURLY ADMINISTRATION

AGE GROUP	APPROXIMATE WEIGHT (KG.)	DOSE (MG.)	FLUID VOLUME (C.C.)
Premature infant	1.5	15	15
Newborn	3.5	35	35
1 year	10.0	100	100
5 years	20.0	200	200
10 years	32.0	320	320
Large children	50.0	500	500

schedules for several age groups are presented in a simple table for convenient reference.

In conclusion, it is recommended that a terramycin concentration of 1 mg. per cubic centimeter be routinely employed with a dosage of 10 mg. per kilogram body weight every twelve hours in average infections; in more serious conditions higher dosages of 20 to 25 mg. per kilogram every eight to twelve hours may be necessary. We feel that the administration of this broad-range antibiotic by hypodermoclysis is a useful and practical mode of therapy that can play a very worthwhile role in the successful management of infectious disease in childhood.

The authors wish to express their thanks to Dr. A. R. English and his colleagues in the Biochemical Research and Development Laboratories, Chas. Pfizer & Company, Inc., for performing the terramycin serum assays, and to Dr. S. P'an, of the Pharmacological Laboratories, for allowing us to review his animal data. The terramycin used in this study was generously supplied by Chas. Pfizer & Co., Inc.

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A STATISTICAL STUDY OF OTITIS MEDIA IN CHILDREN

II. The Antibiotic Era

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IN 1940 I published a study[1] entitled as above, which, had I been prescient concerning the discovery of antibiotics and improved chemotherapeutic agents, I might well have subtitled "The Era of Judgment Alone." Even in those days, pediatricians were usually more conservative in their attitude toward the therapy of otitis media than their colleagues in the otological specialty, and many agreed that myringotomy could well be reserved for those cases that did not respond to the palliative measures of the day: rest, warmth, nose drops, and pain-relieving ear drops and anodynes. That point of view was expressed beautifully by Brennemann[2] over twenty years ago, and my original study was designed to support statistically, if justified, the conservative opinions which he voiced and with which I agreed.

It was shown in the cases reported at that time that conservative care promoted more rapid recovery, and that mastoiditis occurred only in those children subjected to myringotomy, so it would seem reasonable to assume that now, with potent antibiotic drugs available, myringotomy should much less often be required. Were this thesis generally accepted, the present study would be redundant, but the idea that surgical evacuation of secretion is a sine qua non of effective therapy is slow to die. In our own community an acute, bulging eardrum, seen by an otologist, is opened rather promptly, and this practice is sponsored in the literature. Recently, Rutherford[3] stressed the concept that the use of antibiotics without tympanic surgery was the source of epidural abscess, cholesteatoma, perisinus abscess, and chronic perforation with subsequent loss of hearing. Her report is not accompanied by case reports or statistical data. I can only answer that in my practice, over a period of more than twenty years, I have never met with the first three complications; chronic perforation has been seen only in children whose drums have been incised, and the few cases of chronic deafness that I have seen have seemingly been unrelated to otitis media. Some of the writers on this subject are ambiguous; for example, Livingston[4] states that acute catarrhal otitis media "a transient stage between tympanic catarrh and acute purulent otitis media . . . usually subsides quickly after myringotomy," but that in the case of its suppurative sequel conservative measures may be employed for a day or two before resorting to incision of the tympanic membrane.

Som[5] is also confusing when he asserts that "paracentesis of the eardrum, formerly one of the most frequent operative procedures, is now rarely necessitated," and on the following page reverses himself by accepting as "an indication for liberal paracentesis, the bulging eardrum, with or without chemotherapy."

The texts devoted to otolaryngology are generally rather dogmatic, insisting as does Woodward[6] that "myringotomy should always be carried out as soon as one notes the increasing accumulation of gas and pus . . . which is manifested by bulging of the drum

membrane," whereas the pediatric tests often agree, as does Nelson[7] that there is "a growing tendency toward conservatism. Bulging per se, even in the presence of fever, is not generally regarded as an indication (for myringotomy), since, in the majority of instances, recession will take place without rupture of the membrane."

I believe that the data that follow substantiate Nelson's statement.

The cases presented in this study were all seen by me, in private practice, during the six and one-half years from January, 1946, through June, 1952. During the first two years after my return from service only the sulfonamides (almost invariably sulfadiazine) were employed, chiefly because of economic factors. The choice of therapy during the most recent twenty-four months is presented in tabular form and is discussed in the portion of this article concerning treatment. The only cases omitted from this series are those infants who were brought in for routine examination and were found to have inspissated pus within the canal, the result of unrecognized otitis media occurring during the few weeks since previous examination. These are not uncommon. Pain and fever have apparently been of short duration, and the spontaneous evacuation of pus seems to be innocuous and healing is prompt.

In Table I the age incidence of the disease is indicated. The chief importance of this is the decrease in frequency of otitis media after the fourth year. This parallels our experience with upper respiratory infections, and also tends to explain why tonsil removal is most often urged at this age in order to prevent recurrences of otitis media. In this regard, I can only echo the experience of Kaiser[8] that "it cannot be demonstrated that the tonsils are often a causative factor in such infections as the common cold, otitis media, sinusitis and laryngitis."

TABLE I. AGE INCIDENCE

AGE (YR.)	NO.	%
Under 1	174	16.8
1-2	183	17.7
2-3	132	12.8
3-4	134	13.0
4-5	100	9.7
5-6	112	10.7
6-7	76	7.4
7-8	46	4.5
8+	74	7.2
Total	1,031	99.8

Table II is presented as a matter of interest only. It coincides with the incidence of the common cold in this vicinity.

TABLE II. MONTHLY INCIDENCE (1946-1951)

	NO.	%
Jan.	103	11.8
Feb.	105	12.1
March	119	13.7
April	100	11.5
May	78	9.0
June	47	5.4
July	17	2.0
Aug.	11	1.3
Sept.	28	3.2
Oct.	34	3.9
Nov.	87	10.0
Dec.	141	16.2
Total	870	100.1

Table III, I believe, is important. The number of myringotomies was reduced to a minimum; the number of ears that subsequently drained was more than halved. To the best of my knowledge, no complication obtained in this group.

Table IV shows the type of medication employed. The term sulfa signifies Gantrisin or triple sulfonamides. In a few cases the broad spectrum antibiotics were given.

Table V gives the tabulated response of forty-four physicians in various

TABLE III

	1932-1940 SERIES	1946-1952 SERIES
Uneventful recovery	297 (50.4%)	875 (84.5%)
Myringotomy	199 (33.8%)	13 (1.3%)
Discharging when first seen	60 (10.2%)	126 (12.1%)
Subsequent drainage	32 (5.4%)	22 (2.1%)
Total	588 (99.8%)	1,036 (100.0%)

In the earlier series there were sixteen cases of mastoiditis, requiring operative procedure. All these cases were in children who had been subjected to myringotomy.

In the present series there was *no* case of mastoiditis. One infant who gave no evidence of middle ear infection developed a mastoid infection spontaneously and was operated upon in a metropolitan hospital.

TABLE IV. MEDICATION USED DURING THE MOST RECENT TWENTY-FOUR MONTHS COMPRISING 393 CASES (516 EARS)

Sulfa only	53
Penicillin injection only	95
Penicillin orally only	103
Penicillin injection followed by oral sulfonamides	85
Oral penicillin in combination with sulfonamides	43
All other cases	14

TABLE V

	MYRINGOTOMY EMPLOYED		
	FREQUENTLY	INFREQUENTLY	ALMOST NEVER
E.N.T. specialists	5	4	2
General practitioners	0	3	11
Pediatricians	0	2	17

ANTIBIOTICS (FIRST CHOICE)	GENERAL PRACTITIONER	PEDIATRICIAN	E.N.T. SPECIALISTS
Penicillin (injection)	8	10	8
Penicillin (oral)	1	3	2
Sulfonamides	3	6	1
Penicillin-sulfa combinations	2	0	0

cities east of the Mississippi to two questions:

Do you employ myringotomy frequently, infrequently, or almost never? —and—

What is your most often used antibiotic or chemotherapeutic drug?

A space was left for remarks, and these were naturally in support of the answering physician's usual practice. I was most impressed by the words of Dr. Henry Merriman, an otologist of Waterbury, Conn., who wrote, "I do a myringotomy for (1) pain over 24 hours, (2) continued fever, (3) if the drum is bulging and is not returning to normal after adequate therapy." I am in total accord with these principles. The corollary is, that adequate therapy, promptly employed, will almost invariably reverse all three indications quite rapidly.

In the original study other factors were analyzed. At that time no preceding illness was evident in 71 per cent of the cases. This figure is now even higher because no case in this series followed either pneumonia or scarlet fever. The usual number of visits required was analyzed. This figure is now down to the irreducible figure *one*. In spite of the routine that many physicians follow, of checking the drum every few days until normality is established, I have not felt that an injustice has been done, when adequate therapy has been administered or prescribed, if one requests a telephone report after forty-eight hours, and if fever and discomfort are not present to advise accordingly. This may not be wise in the case of outpatient clinic practice, but with an informed clientele one will be advised promptly in event of trouble. Nor can I now evaluate the mean number of days of illness. In almost every case the child is well within forty-eight hours.

THERAPEUTIC PRINCIPLES

I am convinced, and I believe that these results indicate that myringot-

omy is, in most cases, an unnecessary procedure. I have found that either sulfonamide therapy or the use of penicillin is rapidly effective in returning the acute ear to normal. I still employ ear drops; 5 per cent phenol in glycerin is most effective, and eminently safe. I have almost entirely discontinued the use of nose drops either prophylactically or therapeutically. It has been demonstrated that their long-time employment causes ciliary damage, that antiseptic substances may give local reactions, and I believe that they may initiate aural or sinus infection when none existed prior to their use.

Studies by Keefer[9] and others have proved that penicillin is effective when ingested. Therefore, unless the baby is very young or the child is vomiting, refractory, or acutely ill, I give medication by mouth whenever possible. If penicillin is to be injected I give a large dose since I feel that in that way bacteriostasis is best obtained, and allergic reaction is no more likely than were a smaller dose employed; even in a small baby I use a combination of 300,000 units of procaine penicillin together with 200,000 units of penicillin G, freshly prepared at the bedside. The one dose is usually adequate, nor have I had any adverse reaction from this.

In older, cooperative children I avoid injection, both from the standpoint of needless pain and the lesser likelihood of reaction when the substance is given orally. A palatable solution is given, 100,000 to 200,000 units, four times daily, doubling the first two doses. Often this is combined with Gantrisin or one of the triple sulfonamide preparations, giving 1 to 1½ grains per pound of body weight each day.

Except in very young infants, when the single huge dose of penicillin by injection is given, I ask that the oral medication be continued at least four days. If not so advised the parent will often discontinue therapy as soon as the symptoms subside.

In event that recovery is not prompt, a change from one therapeutic agent to another is indicated; until we know more about the possible antagonism between penicillin and the broad spectrum antibiotics it may be as well to give one at a time.

SUMMARY

A statistical study of otitis media, based upon 1,031 cases seen in private practice during the past six years, has been presented.

It is felt that evaluation of the results has justified the use of conservative measures in the treatment of otitis media in children.

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COMPLETE TRANSPOSITION OF THE GREAT VESSELS

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THE development of surgical operations, designed to alleviate the functional disturbances produced by various congenital malformations of the heart, has emphasized the importance of accurate differential diagnosis of developmental anomalies. Complete transposition of the great vessels represents one of the serious developmental defects which may be compatible with life for sufficient periods to allow surgical intervention. Techniques are available which may be beneficial such as the Blalock or Potts operation and surgically induced interatrial septal defects. In most cases, the prognosis becomes so grave that conservative treatment has little to offer and corrective surgery offers the only hope of survival. However, transposition of the great vessels must be differentiated from other lesions, having a more favorable outlook. The clinical picture of this deformity is so distinctive that definitive diagnosis can generally be made with confidence.

EMBRYOLOGY

During embryological development, the convoluted cardiac tube is converted into a four-chambered heart by the elaboration of three partitions which divide the common atrium, the ventricular chamber, and the truncus arteriosus. The septa which separate the atrial and ventricular cavities tend to lie in a single plane, but the truncus arteriosus and conus region are separated into a pair of arterial trunks by the spiral aortic-pulmonary septum.

Beginning at the bifurcation of the aorta and pulmonary arteries, a pair of ridges form on opposite sides of the cylindrical truncus arteriosus and spiral downward toward the ventricles. Growing inward toward the axis of the cylinder, these ridges fuse into a single septum which executes a spiral of 180° and swings into line with the upper edge of the interventricular septum (Fig. 1, *A*). The spiral septum accounts for the manner in which the major arterial trunks intertwine. The pulmonary artery arises from the right ventricle, passes anterior to the aorta, and emerges on the left of the mediastinum. The aorta lies behind the pulmonary artery and appears on the right side of the mediastinum before arching posteriorly to a position along the left side of the thoracic vertebrae.

Complete transposition of the great vessels has been attributed to a number of complex embryological factors,[1, 2, 3] but it can be schematically represented as due to the development of a straight aortic-pulmonary septum.[4] Thus, the arterial trunks lie parallel as they leave the respective ventricular chambers: the right ventricle emptying into the aorta and the pulmonary artery

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arising from the left ventricle (Fig. 1, *B*). The parallel arrangement of the arterial trunks persists in the fully developed heart (Fig. 1, *C*).

FUNCTIONAL EFFECTS

If the arterial trunks are transposed, venous blood from the systemic circulation is ejected by the right ventricle into the aorta for redistribution to the systemic capillaries. Oxygenated blood returning from the lungs enters the left ventricle and is recirculated through the pulmonary capillaries. Venous blood may enter the pulmonary circuit for oxygenation only through defects or shunts between the systemic and pulmonary circuits. Oxygenated blood, largely confined to the pulmonic vessels, can reach the tissues only by reverse flow through these same shunts. It is apparent that survival depends upon continued patency of communications between the two circuits, e.g., defects in the interatrial or interventricular septa or persistent patency of the ductus arteriosus. The quantity of oxygenated blood entering the systemic circulation is generally small and cyanosis is extremely severe, beginning immediately after birth. The supply of oxygen to the body as a whole is barely sufficient for survival, so growth and development are retarded. Coronary arteries, arising from the root of the aorta, conduct essentially venous blood to the myocardial fibers. The rapid progressive cardiac enlargement which begins shortly after birth is due in part to this unfavorable situation. Further, the right ventricle, which normally pumps blood through the low resistance pulmonary circuit, operates

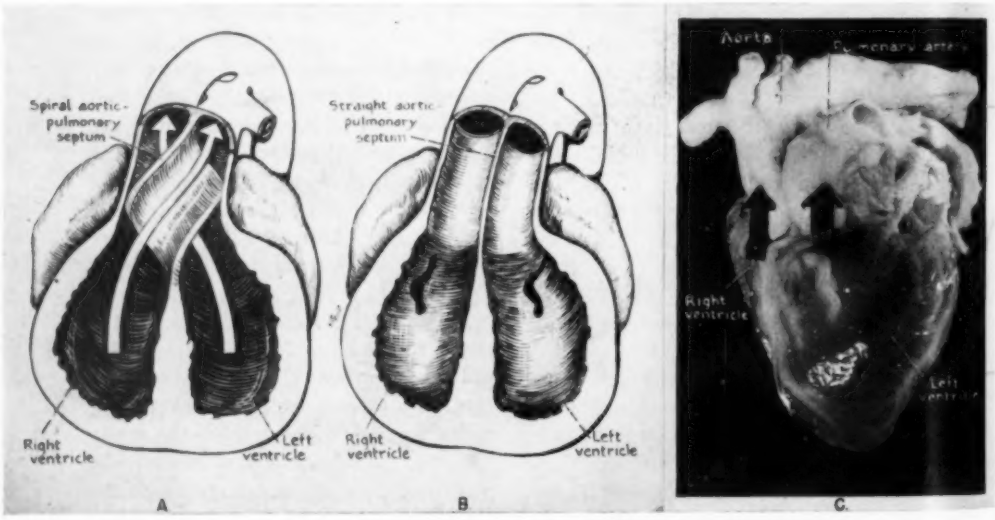

Fig. 1.—The embryological origin of complete transposition of the great vessels. *A*, The normal aortic-pulmonary septum executes a spiral of 180° dividing the truncus arteriosus into the intertwining aorta and pulmonary arteries. *B*, Complete transposition of the great vessels may be schematically represented as due to a straight aortic-pulmonary septum so that the aorta arises from the right ventricle and the pulmonary artery emerges from the left ventricle. *C*, In complete transposition of the great vessels, the aorta and pulmonary artery are parallel as they leave the heart as would be expected if the truncus arteriosus were divided by a straight aortic-pulmonary septum.

against the high resistance of the systemic circulation and becomes progressively enlarged and hypertrophied as the systemic blood pressure rises. In contrast, the left ventricle may be hypotrophic.

CASE REPORTS

The first case was a female child who had moderately severe cyanosis since birth. At 4 months of age there was no heart murmur, the chest was clear; electrocardiograms revealed right ventricular preponderance; teleroentgenograms revealed a heart which was apparently about normal in size with a narrow mediastinal shadow in the posteroanterior position (Fig. 2, A). In the left anterior oblique position the upper mediastinal shadow was broad.[5] Blood studies disclosed the following: hemoglobin 17.8 grams, red blood count 5.4 million, white blood count 8,500 with normal distribution. The liver was extended 2 to 3 cm. below the costal margin in the right midclavicular line. At 28 months her height was 80 centimeters, weight 8 kilograms, and she was able to sit quietly but could not walk. At this time she developed cardiac decompensation following an upper respiratory infection. Systemic venous congestion, dyspnea, and peripheral edema were prominent. Roentgenograms showed pronounced enlargement of the cardiac silhouette with prominent vascular markings in the lung fields. Electrocardiograms revealed right ventricular preponderance and a Q_3T_3 pattern was interpreted as indicating myocardial ischemia. Therapy with digitoxin produced marked symptomatic improvement but the heart remained enlarged (Fig. 2, *B*).

Her condition remained fairly good for about five months when cardiac decompensation recurred, again following an upper respiratory infection. After maximal clinical improvement had been attained with digitoxin, the cardiac enlargement was definitely more pronounced (Fig. 2, *C*). In view of the ominous signs of impending deterioration, surgical production of an artificial shunt between the systemic and pulmonary circuits appeared to offer the only hope for survival. Since progressive spontaneous closure of the ductus arteriosus frequently contributes to the deterioration of such a patient's condition, surgical production of a systemic pulmonary shunt was considered the only hope for survival. That the child had lived for nearly three years was considered sufficient evidence for the presence of an intracardiac shunt (e.g., an interatrial septal defect). The immediate outlook for a patient with transposition of the great vessels is much more favorable so long as the ductus arteriosus and interatrial septal defect are both functioning to permit exchange of blood between the systemic and pulmonary circuits. On this basis, a Blalock operation was performed at the age of 34 months. Postoperatively her condition was strikingly improved for three days at which time she abruptly developed severe cyanosis, dyspnea, liver enlargement, crepitant râles in the bases of both lungs, and expired after about twelve hours.

Post-mortem examination revealed a thrombus filling the left subclavian artery and extending through the surgically induced anastomosis into the left pulmonary artery. The right ventricle was dilated and hypertrophied. The only functional shunt between the pulmonic and systemic circuits was through a small patent foramen ovale. The ductus arteriosus could not be found. Microscopic sections revealed hypertrophy of the myocardial fibers, but no evidence of infarction or myocarditis.

Another case, with similar history and clinical signs, was studied by means of cinefluorographic angiocardiography, at the age of 16 months, in preparation for surgical intervention because her condition was rapidly deteriorating. Diodrast* (70 per cent)

*Generously supplied for this study by the Winthrop Stearns Company.

Fig. 2.—Progressive cardiac enlargement, characteristically associated with complete transposition of the great vessels, is illustrated by teleroentgenograms taken at (*A*) 4 months, (*B*) 28 months and (*C*) 34 months. Note the narrow mediastinal shadow particularly in *A*.

was injected through a polyvinyl catheter fixed in the left jugular vein. The course of the opacified blood was followed for 10 seconds by cinefluorographic recording on 35 mm. film exposed at fifteen frames per second using equipment* which has been previously described.[3] A series of photographic prints reproduced from this film has been retouched to emphasize the salient features. In the first frame (Fig. 3, *A-1*) opacified blood had passed through the catheter into the superior vena cava and partially filled the right atrium. Small quantities of Diodrast appeared to pass from the right atrium interatrial septal defect into the left atrium in frames *A-2* and *A-3*, prior to the filling of the right ventricle. The tricuspid valves began to open in frame *A-4*, and the right ventricular chamber was filled in the next frame (*B-1*). Right ventricular contraction began in frame *B-3* since Diodrast appeared in the root of the aorta and in the next frame the arch of the aorta became opacified. During the next contraction the right ventricle and aorta were more clearly delineated (*E-1*). This sequence of pictures was exposed during an interval of 1⅓ seconds. During the remainder of the ten-second period the picture was essentially unchanged. At no time was there sufficient radiopaque material in the left ventricle or pulmonary artery to produce distinct opacification. Diodrast must be present in fairly high concentration to be recorded by this technique. This film was interpreted as follows: complete transposition of the aorta and pulmonary artery, associated with an interatrial septal defect. The ductus

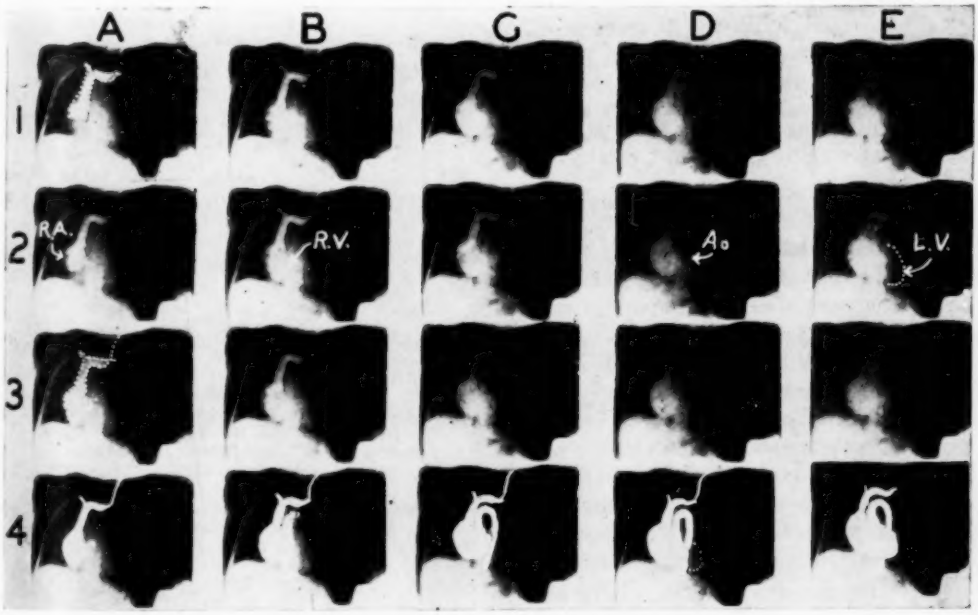

Fig. 3.—Angiocardiography, recorded on 35 mm. film at fifteen frames per second by the cinefluorographic technique, demonstrated conclusively that the right ventricle communicated directly with the aorta and that there was minimal admixture of blood between the systemic and pulmonary circuits (see text).

*X-ray equipment used for this project was provided by the General Electric x-ray corporation.

arteriosus was considered to be obliterated.

The patient tolerated the angiocardiography without apparent difficulty, but thirty-six hours later respiration suddenly stopped and she expired. The immediate cause of death was not determined. Post-mortem examination confirmed the presence of complete transposition of the great vessels. The ductus arteriosus was obliterated and the only obvious communication between the systemic and pulmonary circulations consisted of three small interatrial septal defects roughly the size of a pin head or match head. Stretching the septum increased the diameter of the largest to about 3 to 4 mm.

SUMMARY

Complete transposition of the aorta and pulmonary arteries produces a characteristic clinical pattern consisting of (1) cyanosis which begins immediately after birth, (2) increased blood flow and blood content in the pulmonary vessels, (3) right ventricular preponderance, (4) progressive cardiac enlargement, (5) retardation of growth and development, (6) angiocardiographic evidence of continuity between the right ventricle and the aorta.

Among the cyanotic group of congenital deformities the appearance of cyanosis at birth is rarely encountered except with transposition of the great vessels.[6] Except in this condition cyanosis early in life is almost invariably associated with obstruction to pulmonary blood flow and reduced lung markings on teleroentgenograms. Judging from the cinefluorographic picture presented, a single teleroentgenogram taken from 2 to 5 seconds after beginning the injection of Diodrast should provide a definitive diagnosis of complete transposition of the aorta.

Cases of complete transposition of the great vessels have much better prognosis if multiple shunts exist. If the only site of exchange of oxygenated and venous blood consists of an interatrial septal defect, the outlook is so grim that surgical intervention provides the only hope for survival. The distinct improvement in one case from a Blalock operation indicates that this may offer at least palliative relief.

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DEFORMITIES OF THE THORAX OF CONGENITAL OR DEVELOPMENTAL ORIGIN

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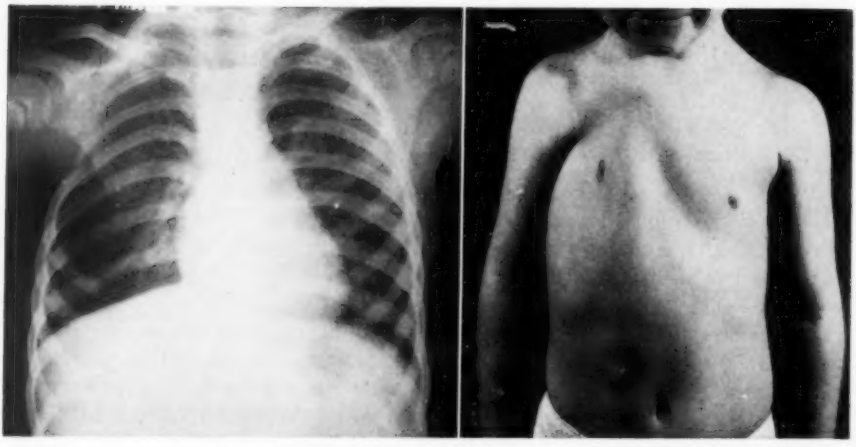
SINCE the historical paper by Brown[1] on funnel chest in 1939 a fairly extensive literature on the effects and treatment of this deformity has appeared. There are, however, numerous other congenital or developmental deformities of the thorax about which little or nothing has been written and which are ignored because it is thought that they are of minor importance and are not amenable to treatment. Many of these conditions are deforming and unsightly and some are crippling and disabling. A psychological problem of considerable magnitude is often present. Treatment is ineffectual for some and unnecessary in others, but in many cases proper surgical treatment can greatly improve the condition or correct it completely.

Some of these deformities, notably funnel chest, are apparent at birth and may be called congenital. Others, as in the case of pigeon breast, are not present until growth of the child makes them apparent. These may be said to be developmental. Disease is not a factor in any of the deformities discussed in this paper. For purposes of classification they may be divided into two groups. In the first group are those deformities due to absence or malformation of bony structures. In the second group the bones are apparently normal and the deformity is probably caused by abnormal growth and the abnormal pull of the attached muscles.

In the first group belong the cases having absent ribs, incomplete ribs, fused ribs, forked ribs, and supernumerary ribs. The forked ribs and extra ribs seldom cause any trouble and are found by chance after x-ray examination. If the forked part of the rib is at the cartilaginous end it may completely escape detection. Occasionally a rib will be found that forks at its anterior end and has one fork fusing with the adjacent rib.

When ribs are rudimentary or absent the resultant deformity is usually apparent, not only because of the bony abnormality but also because the muscles which would ordinarily attach to the defective rib are absent or malformed. Fig. 1, *A* shows the x-ray of such a case. It is seen that the anterior two-thirds of ribs 2, 3, and 4 on the right side are absent. This permits the lower ribs on that side to drop down and in, causing the scapula to override the vertebral column when the arm hangs at the side. Fig. 1, *B* is the photograph of the little girl which shows that the right pectoralis major muscle has only its clavicular portion and that the nipple on that side is drawn upward and distorted, a condition which will become more noticeable as the girl develops.

In another case of a similar defect on the left side in a 4-month-old infant the anterior ends of ribs 3 and 4 were absent and the fifth rib dropped down. This left the heart without any bony protection and its pulsations were so visible through the thin chest wall that the obstetrician, pediatrician, and parents were quite apprehensive. The



A. *B.*

Fig. 1.—Congenital defect in ribs 2, 3, and 4. *A*, Roentgenogram showing defect in anterior and lateral extent of upper ribs. *B*, Narrowing of shoulder girdle on right and absence of costal portion of pectoralis major.

Fig. 2.—Severe scoliosis due to maldevelopment and fusion of ribs on left.

baby, however, was entirely unconcerned and is now an active 3-year-old child developing in a normal manner. The chest wall, still without bony covering, has stiffened and seems to provide adequate protection.

The defect left by absent or maldeveloped ribs seldom requires any treatment. The normal growth of the child will compensate to a certain extent for the deformity. If it does not do so some plastic operation may be used after puberty. Such an operation will depend on the individual case and certainly cannot be standardized.

The fusion of the anterior ends of the ribs, such as occurs in forked ribs, is of small import and needs no treatment. Fusion of the posterior ends of the ribs, especially when the ribs are more or less rudimentary, as is usually the case, is quite another matter, and can produce some of the most crippling deformities that are encountered. The magnitude of the deformity depends upon the extent of the fusion. With respect to the elongation of the vertebral column during growth, the fused ribs act as a vector which curves the spine toward the side of the fusion. At birth there is little or no deformity but as growth ensues scoliosis develops and increases while growth continues, or until corrected. Fig. 2 shows such a case.

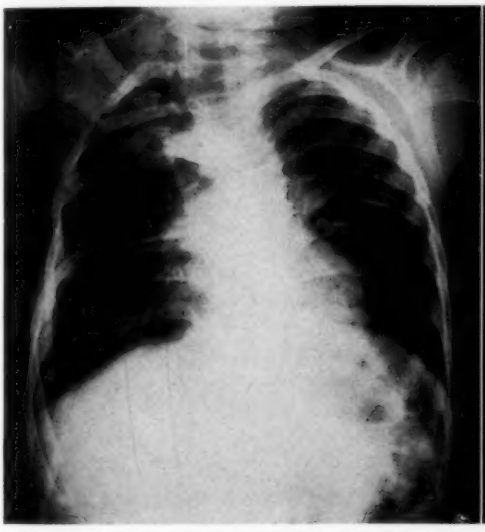


Fig. 3.

Fig. 4.

Fig. 3.—Multiple deformities of thorax: maldeveloped and fused ribs, hemivertebrae, displaced scapula, and spina bifida.

Fig. 4.—Photograph of patient in Fig. 3 showing elevated shoulder, protrusion deformity of chest (due to discrepancy in length of upper and lower ribs), and false funnel chest. This boy also lacked sphincter control because of low spina bifida and had clubfeet.

The patient was a girl 6 years of age with a progressive scoliosis which produced pressure on the lung of the concave side so as to greatly impair the pulmonary function, and to limit the child's activities seriously. To correct the condition it was first necessary to

resect the fused ribs. Orthopedic correction (Dr. John R. Cobb) of the scoliosis was then commenced by applying a plaster jacket divided in such a manner as to straighten the vertebral column when the halves were wedged apart. Spinal fusion is considered ultimately. Obviously the earlier that correction is initiated in such a case the greater the chances for a successful correction of the deformity.

When there is one congenital deformity it is common to find others. An extreme case in point is depicted in Figs. 3 and 4. The patient, a 3-year-old boy, was brought to the hospital because of clubfeet. The chest deformity was noted and x-ray of the chest showed absence of at least one rib, the fusion of four or five ribs which are also rudimentary, hemivertebrae and spina bifida in the dorsal region, and a defective scapula. The photograph (Fig. 4) shows an anterior protrusion deformity of the chest and a false funnel chest. The right shoulder was elevated because the small scapula was caught behind the highest normal ribs in much the same fashion as after a five- or six-rib thoracoplasty. It was not a Sprengel's shoulder as first suspected. While the clubfeet were being corrected several operations were performed on the chest which flattened the protrusion, elevated the depression, and resected the angle of the scapula, allowing the shoulder to drop to a normal level. During these hospital confinements the nurses complained because the 3-year-old boy made no attempt to use a bedpan or urine bottle, in spite of lectures and scoldings. It was not until then that a rectal examination was done which, of course, showed a flaccid rectal sphincter, obviously due to a low spina bifida which had been overlooked. The spina bifida was then operated upon (Dr. T. I. Hoen) and a year later the child had fair control of his sphincters, his various deformities were greatly improved or corrected, and he gives promise of developing into a useful citizen.

Another type of congenital deformity is caused by the failure of the two lateral halves of the sternum to fuse.

Fig. 5.—Unilateral protrusion deformity of chest.

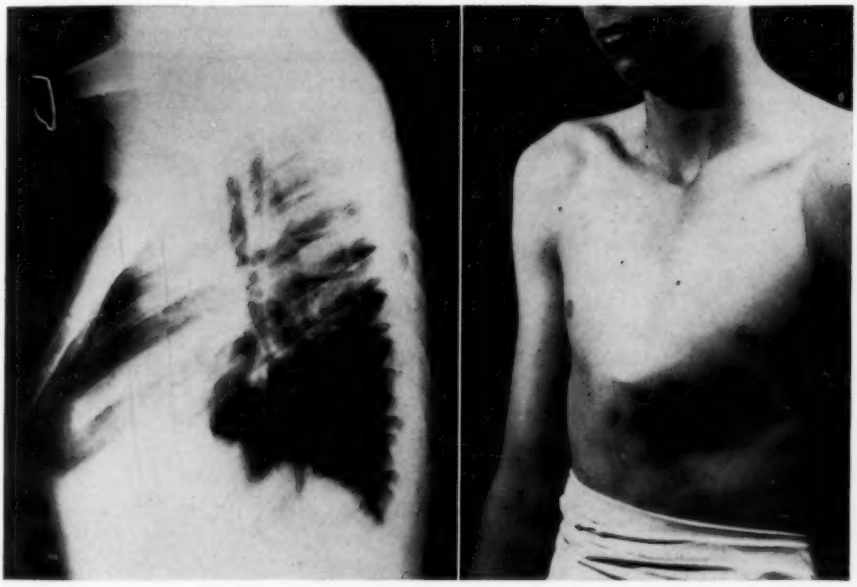
Maier and Bortone[2] have reported the successful surgical treatment of such a case. In most instances, however, the defect is accompanied by ectopia cordis which is incompatible with life.

In the second group of chest deformities the bony structures appear to be normal and the deformity seems to be caused by muscle pull, growth of

bone, or both. Funnel chest obviously belongs in this group. The protrusion deformities, of which pigeon breast is one, are also included in this classification as will be explained below.

The protrusion deformities fall into two main classes: those with protrusion in the midline, i.e., with a prominent sternum, and those in which the protrusion is to the left or right of the sternum. The protrusion may also be below the level of the sternum and thus in the costal arch. The midline deformities are further divided into those with an arched sternum where the midpoint of the sternum is the most prominent, and those with an oblique sternum in which the xiphoid is the most prominent. The arched sternum may produce an apparent depression of the xiphoid which has been mistaken for funnel chest (Fig. 4) but the distance between the xiphoid and vertebrae is not shortened and there is no displacement of the heart.

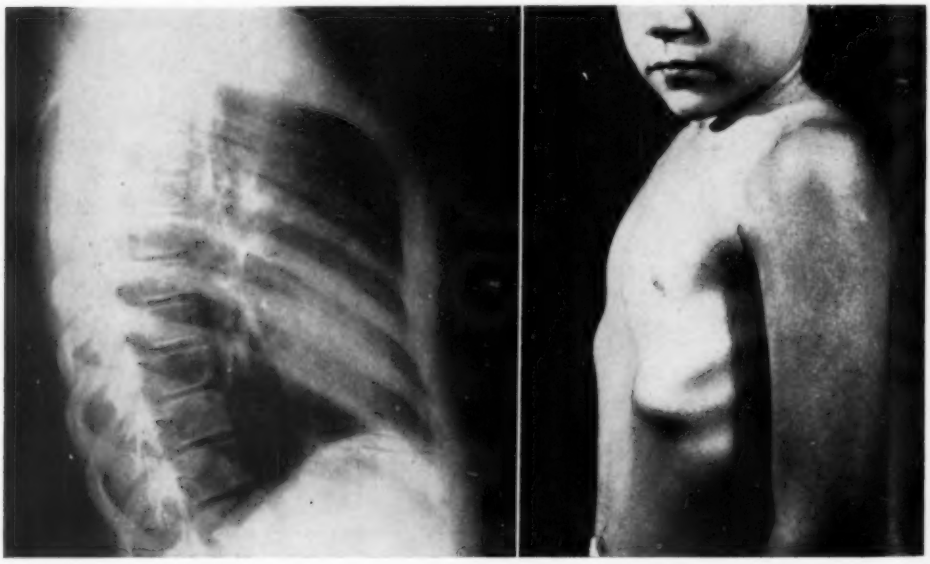
The etiology of the protrusion deformities is obscure. Brodkin[3] considers the sternal protrusions to be the result of diaphragmatic abnormality, but this seems inadequate to explain the condition. However, theoretically, a diaphragmatic or other muscular restraint coupled with overgrowth of the ribs could account for it. The growing force of the rib thus restricted causes it to buckle at the costochondral junction, its weakest point. If the overgrowth is on one side only, there will be a protrusion of the costochondral junctions and a unilateral deformity



A. *B.*

Fig. 6.—Protrusion deformity of sternum with xiphoid at apex of deformity. *A*, Lateral roentgenogram showing marked prominence of xiphoid. *B*, Photograph of patient showing pyramidal deformity.

(Fig. 5). If the ribs of both sides grow excessively, the buckling of the ribs will force the sternum forward into a midline deformity. If the central tendon of the diaphragm grows at the same rate as the ribs, the xiphoid will be the most prominent point of the protrusion (Fig. 6, *A* and *B*). If the central tendon does not keep pace with the ribs, the sternum, thus restrained at its lower end, will arch forward (Fig. 7, *A* and *B*). If overgrowth occurs in ribs below those which attach to the sternum, the protrusion appears in the costal arch and may be associated with a transverse groove (Fig. 7, *B*). This deformity may be unilateral or bilateral.



A. *B.*

Fig. 7.—*A*, Pigeon breast, arcuate type of deformity. *B*, Transverse groove and costal arch protrusion involving eighth rib, associated with moderate arcuate deformity.

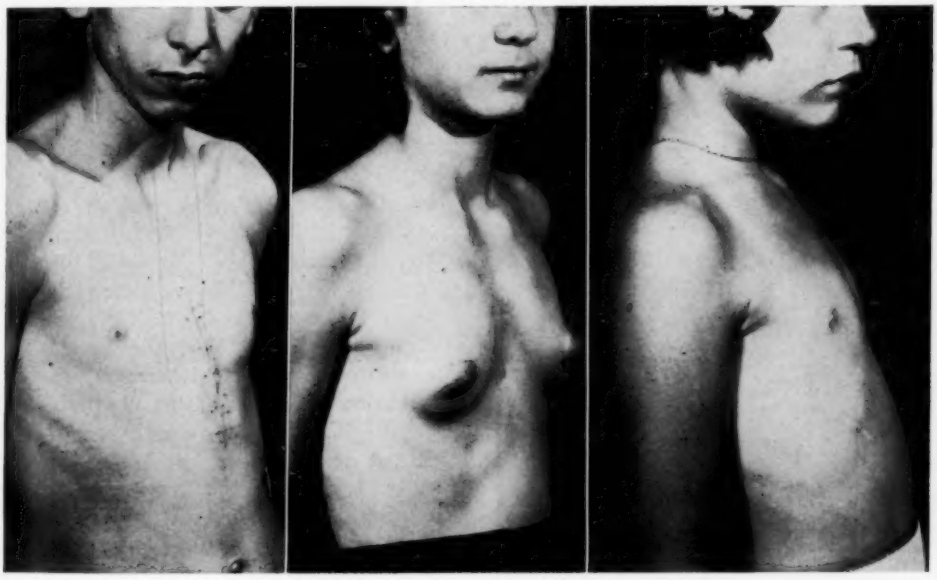
Since growth is the factor which determines the deformity it follows that the deformity is rarely present at birth. It is seldom noticed until after infancy and usually not until the child is more than 5 years old. By the time the deformity is noticeable enough to make the parents or patient desire correction he may be near the age of puberty.

In determining the physiological effects of a congenital or developmental deformity the statement of the patient cannot always be taken at its face value because he has never known what it is to be normal. Many, of course, never do have any symptoms but, on the other hand, certain symptoms occur with sufficient regularity to suggest a causal relationship. These are respiratory infections that persist too long and are variously called bronchitis, asthma, or pneumonia by the patient or parent; failure to gain weight properly; easy fatigability; and dyspnea and tachycardia. Not infrequently the psychological distress

caused by the deformity overshadows everything else and may of itself produce physiological disturbances.

Whether or not to advise surgical correction of the deformity is a difficult decision to make. In general, it is safe to say that surgical correction should be undertaken if the patient earnestly desires it or if respiratory or cardiac symptoms are present. Under such circumstances the results are often dramatic. In competent hands the risk of the operation is slight.

tion of the protruding portions of the ribs involved, and may best be done in two stages because of the paradoxical respiration which occurs if numerous ribs are resected at one time. As regards the sternal deformity, the involved portions of the cartilages are resected subperichondrially and the protruding portion of the sternum is resected subperiosteally, which implies separation of the xiphoid but not division of the substernal ligament. The periosteum remaining then drops down



A. *B.* *C.*

Fig. 8.—*A*, Surgical result in patient shown in Fig. 6, *B*. *B*, Surgical result in patient shown in Fig. 7, *A*. *C*, Surgical result in patient shown in Fig. 7, *B*.

The operation for the correction of protrusion deformities is based on one of the principles of thoracoplasty, viz., that a rib resected subperiosteally will regenerate in the position taken by the stripped periosteum. When the protrusion is lateral this involves subperiosteal and subperichondrial resection into a normal position where the new bone regenerates (Fig. 8, *A*, *B*, and *C*).

The patients have surprisingly little reaction to the surgical procedure and are usually out of bed the next day and home a week after completion of the surgery. Of the sixteen patients

operated upon there have been no deaths nor serious complications and the late results have been satisfactory.

Funnel chest (pectus excavatum) is the other congenital deformity produced by abnormal muscle pull. This has been in the medical literature for more than three centuries but it remained an enigma until 1939 when Brown[1] recognized the cause and described a rational treatment for it. Since then many more articles have appeared on the subject.

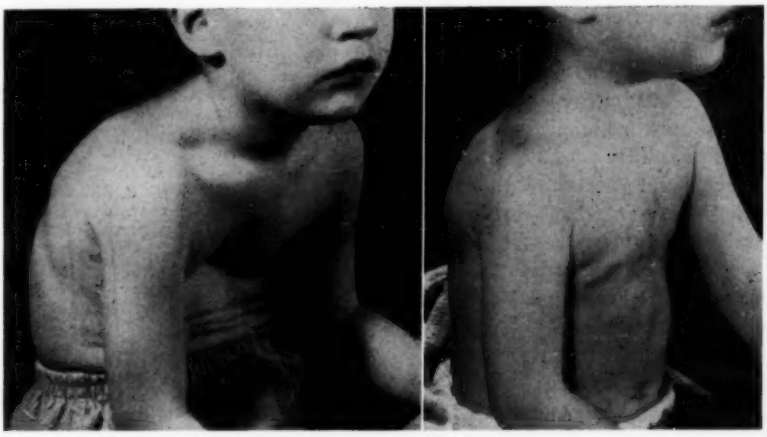
Fig. 9.—Lateral roentgenogram of funnel chest.

As the name implies, the deformity is a funnel-shaped depression of the anterior chest wall with the apex of the funnel at the xiphoid. The major factor in the production of the deformity is the pull exerted by a short central tendon of the diaphragm which draws the xiphoid backward during inspiration in a direction opposite to its normal movement (Fig. 9). Other less evident factors may also be operative. The deformity is usually noticed at birth and becomes progressively worse as the child grows older.

The pressure of the sternum on the heart rotates it and displaces it into the left chest thereby causing more or less disturbance of its action and frequently producing a murmur. The short diaphragm interferes with the cough so that minor respiratory infections are prone to go on to pneumonitis and chronic bronchitis because the bronchi cannot be cleared of their secretions. In addition to the funnel deformity, round back and poor posture are common (Fig. 10) and the children are likely to be underweight and underdeveloped. In some patients the sternal depression is so small that there are no symptoms, but I believe that where there is a significant sternal depression there are also physiological effects, whether or not the patient recognizes them. Furthermore, the psychological effects of the deformity may be considerable, even though the patient does not feel that he is physically handicapped. Previous communications[4, 5] go into greater detail about the cause and effects of the deformity.

The treatment is surgical. In infants under 14 months of age, before the deformity has become irreversible, a simple operation by which the xiphoid is detached from the gladiolus and the substernal ligament severed may suffice to allow normal development of the chest. Later, when the deformity has become established, a radical procedure is necessary which entails resection of the third to the

seventh costal cartilages on both sides, detachment of the xiphoid, resection of the substernal ligament, and elevation of the sternum by fracture along a transverse wedge osteotomy in the third sternal segment. The sternum is then maintained in this position by temporary external support. Modifications of this procedure have been described by Sweet,[6] Brodkin,[7] Dorner and associates,[8] Ravitch,[9] and others.



A. *B.*

Fig. 10.—Funnel chest with round back. *A*, Before operation. *B*, After operation.

Experience in the late follow-up of our sixty-three cases has led us also to make modifications. Recurrence of the deformity after the simple operation has not been uncommon but, for the most part, the depression has not been bothersome and there have been no symptoms. Three cases, however, required reoperation. For this reason, in cases where we formerly employed the simple operation, we now do a subperichondrial resection of two or more pairs of cartilages close to the sternum and then bend the sternum up, with or without a transverse osteotomy. By using proper instruments and exercising care this can be accomplished without perforating the pleura and hence does not require endotracheal anesthesia. No external support is used.

Our success in this has encouraged us to apply the operation in a more extensive form to those patients in the age group between 14 and 28 months. In the past we have avoided operating on these children because the simple operation is inadequate and the radical operation requires endotracheal anesthesia which too often has to be followed by tracheotomy. But the modified operation without intubation permits surgical treatment at a time when it can produce the best results. However, we do not attempt this operation unless we have a skillful anesthetist who can insert the endotracheal tube promptly should the need for it arise.

Because of one recurrence in the teen-age group we have modified the radical operation so as to overcorrect the deformity and to retain the middle half of the resected costal cartilages somewhat after the method of Sweet.[6]

Except as noted, the results have been good. There have been no fatalities.

SUMMARY AND CONCLUSIONS

Congenital and developmental deformities of the thorax occur in a variety of forms and are classified in two groups.

In the first group are those deformities due to maldevelopment of the bony structures. Some are of little importance but others, especially those due to the fusion of ribs, can produce disabling deformities which need correction.

In the second group are those deformities due to abnormal forces acting on apparently normal bony structures. Funnel chest and the protrusion deformities, such as pigeon breast, are in this group.

The effects of these deformities are discussed and the surgical treatment, when indicated, is outlined.

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CAUSES OF FETAL AND NEONATAL DEATH WITH SPECIAL REFERENCE TO PULMONARY AND INFLAMMATORY LESIONS

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(Concluded from the January issue, page 25.)

BRONCHOPNEUMONIA

Bronchopneumonia was responsible for the deaths of ten infants. All were liveborn infants; their duration of life varied from 17 minutes to twenty-five days. Five infants lived less than twenty-four hours. Six of the infants were males and four were females; nine were Negro and one was white. All but one infant were premature; their weights varied from 820 to 2,900 grams, with an average weight of 1,808 grams.

In addition to the ten infants in whom bronchopneumonia was considered to be the primary cause of death, twenty-six infants and three fetuses had histologic evidence of bronchopneumonia. In the latter group bronchopneumonia was thought to represent a contributory rather than a primary cause of death. These figures do not include infants or fetuses with congenital syphilis since the neutrophilic exudate which is often present in the pulmonary alveoli of these patients may possibly be part of the syphilitic process. Thus, in the entire group of 123 fetuses and infants in whom there was no evidence of congenital syphilis, bronchopneumonia was present as a primary or as a contributory cause of death in thirty-nine (31 per cent); it was present in 40 per cent of the nonsyphilitic liveborn infants and in three of the thirty-four nonsyphilitic fetuses. Twelve of the thirty-six liveborn infants with bronchopneumonia lived less than 12 hours, eighteen lived less than 24 hours, and twenty-six lived less than 72 hours. The average weight of the thirty-nine nonsyphilitic fetuses and infants with bronchopneumonia was 2,092 grams.

The diagnosis of bronchopneumonia can rarely if ever be established by gross examination of the lungs of infants dying within a few days after delivery. Pleural exudate is usually absent, and histologic examination is necessary to differentiate these lungs from those with an intrapulmonary hyaline membrane, excessive aspiration of amniotic debris, or massive pulmonary hemorrhage. Sections should be prepared from all lobes, since the inflammatory exudate may not be present uniformly throughout both lungs. The diagnosis of bronchopneumonia is dependent upon the presence of neutrophilic exudate in the alveolar ducts and alveoli (Fig. 6). Desquamated lining cells or alveolar septal cells are commonly present in the pulmonary alveoli and should not be interpreted as bronchopneumonia.

The majority of infants with bronchopneumonia who die within the first 24 hours after delivery have developed the process in utero, and it is generally agreed that such

examples of intrauterine pneumonia are usually bronchogenic in origin, secondary to aspiration of the contents of the amniotic sac. Some authors feel that aspirated contents of the amniotic sac which are not infected may at times serve as an irritant and call forth a neutrophilic response in the lungs.[54, 61, 117] Substantiation of this view is afforded by the investigations of Macgregor,[68] who obtained significant bacterial cultures from the lungs of approximately one-third of thirty-three dead-born fetuses and liveborn infants with bronchopneumonia. Warwick,[117] using sections stained by Rosenow's modification of Gram's stain, was able to identify bacteria in only one-fourth of the cases of pneumonia in newborn and stillborn infants. Johnson and Meyer[60] were able to demonstrate bacteria in histologic sections of slightly less than one-half of the patients with antenatal pneumonia.

On the other hand, certain findings suggest that many examples of intrauterine pneumonia are bacterial in origin and are due to the aspiration of contaminated amniotic fluid. Johnson and Meyer[60] were able to demonstrate acute inflammation in the placentas and membranes of eleven of thirteen patients with antenatal pneumonia dying prior to delivery; among nine patients with antenatal pneumonia who died in the postnatal period, examination of the placenta, membranes, and umbilical cord revealed acute inflammation in six and syphilitic involvement in two. Moreover, the importance of premature rupture of the fetal membranes as a factor predisposing to the develop-

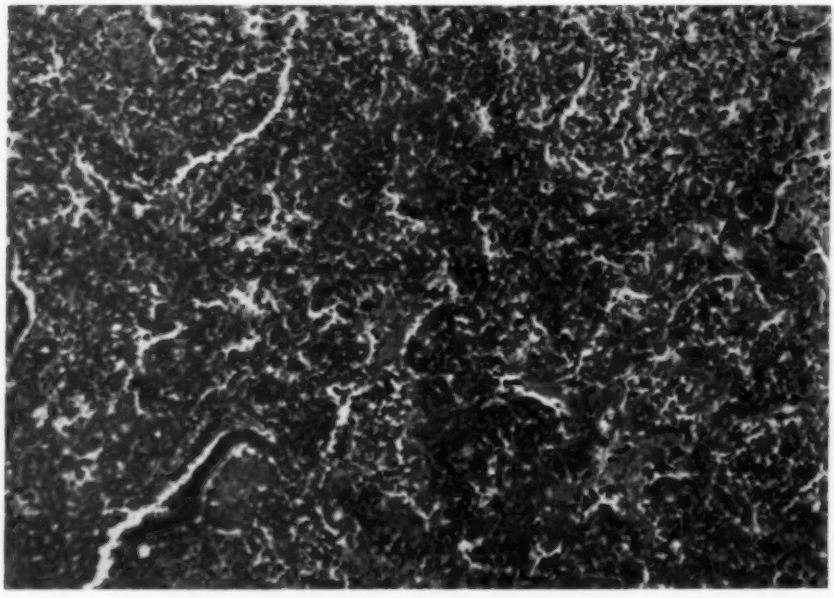

Fig. 6.—Section of lung illustrating bronchopneumonia, from a premature infant 38 hours old. (×200.)

ment of intrauterine pneumonia has been referred to by a number of authors,[19, 33, 64] such premature rupture presumably allowing bacterial contamination of the amniotic fluid. Furthermore, it is well recognized that large amounts of amniotic debris may be found in the pulmonary alveoli in the absence of any inflammatory reaction.

Unfortunately, the role played by bacteria in the pathogenesis of intrauterine pneumonia could not be adequately investigated in the present series, since the length of time that elapsed between the death of the fetuses and infants and the time of post-mortem examination precluded satisfactory bacteriologic studies. Certain observations, however, appear to be relevant to the problem of the pathogenesis of intrauterine pneumonia.

Maternal records indicating the time of rupture of the fetal membranes were available for seventy-two nonsyphilitic fetuses and infants who lived less than 24 hours. Nineteen of these fetuses and infants had bronchopneumonia. Among the fifty-seven fetuses and infants whose fetal membranes had been ruptured less than 24 hours, there were twelve with bronchopneumonia. Among the fifteen fetuses and infants whose fetal membranes had been ruptured longer than 24 hours there were seven with bronchopneumonia (Table V). Although in this small series the difference noted is not statistically significant, it is possible that with a larger series a statistically significant difference might be observed.

Prolonged labor is reported to be a predisposing factor to the development of intrauterine pneumonia. Douglas and Stander,[35] in discussing fetal bacteremia, suggest that organisms present in the vagina at the onset of labor may become invasive and pathogenic during the course of labor. In the present series the duration of labor was reported for eighty-two nonsyphilitic fetuses and infants who lived less than 24 hours. Eleven of the sixty-three fetuses and infants delivered following a labor of less than 24 hours had bronchopneumonia as compared to ten of the nineteen delivered following a labor exceeding 24 hours (Table VI). This difference is statistically significant.

It has been concluded previously that repeated deep intrauterine respiratory movements with resultant

TABLE V. RELATION OF TIME OF RUPTURE OF FETAL MEMBRANES TO INTRAUTERINE PNEUMONIA

TIME OF RUPTURE OF FETAL MEMBRANES PRIOR TO DELIVERY	TOTAL NUMBER OF FETUSES AND INFANTS	FETUSES AND INFANTS WITH BRONCHOPNEUMONIA	FETUSES AND INFANTS WITH NO EVIDENCE OF BRONCHOPNEUMONIA
Less than 24 hr.	57	12	45
Longer than 24 hr.	15	7	8

TABLE VI. RELATION OF DURATION OF LABOR TO INTRAUTERINE PNEUMONIA

DURATION OF LABOR	TOTAL NUMBER OF FETUSES AND INFANTS	FETUSES AND INFANTS WITH BRONCHOPNEUMONIA	FETUSES AND INFANTS WITH NO EVIDENCE OF BRONCHOPNEUMONIA
Less than 24 hr.	63	11	52
Longer than 24 hr.	19	10	9

aspiration of large amounts of amniotic debris are not a normal occurrence and that the presence of large amounts of amniotic debris in the lungs is evidence of fetal anoxia. If the majority of examples of intrauterine pneumonia are bronchogenic in origin, secondary to aspiration of either sterile or infected amniotic fluid in utero, evidences of fetal anoxia should be present with greater frequency in fetuses and infants with intrauterine pneumonia than in those without such pneumonia. In Macgregor's series,[68] pneumonia in fetuses and infants surviving birth not more than 12 hours was invariably associated with aspiration of an excessive quantity of liquor amnii, with or without meconium. Johnson and Meyer[60] found marked aspiration of amniotic fluid in thirty-five of sixty-eight cases of congenital pneumonia. In the present series there were ninety-one fetuses and infants who lived less than 24 hours and who had no evidence of congenital syphilis. Fifteen infants in this group showed evidence of an intrapulmonary hyaline membrane, leaving seventy-six fetuses and infants in whom the presence or absence of excessive amounts of amniotic debris within the lungs could be ascertained.* There was a significant increase in the incidence of bronchopneumonia among those fetuses and infants who had aspirated excessive amounts of amniotic debris when compared to those who had not done so. Conversely, there was a significant increase in the incidence of aspiration of excessive amounts of amniotic debris among fetuses and infants with bronchopneumonia when compared to those without bronchopneumonia (Table VII).

Fetal anoxia is important not only in favoring the development of intrauterine pneumonia but also in predisposing to extrauterine infection of the lungs during the early neonatal period. The atelectatic, congested, and edematous lungs of asphyxiated infants are particularly susceptible to infection.[68, 69] Accordingly, any newborn infant with a history of prolonged labor, premature rupture of the fetal membranes, or signs and symptoms of intrauterine anoxia

TABLE VII. RELATION OF FETAL ANOXIA TO INTRAUTERINE PNEUMONIA

	TOTAL NO. OF FETUSES AND INFANTS UNDER 24 HR. WITHOUT HYALINE MEMBRANE OR CONGENITAL SYPHILIS	FETUSES AND INFANTS WITH SIGNIFICANT ASPIRATION OF AMNIOTIC SAC CONTENTS	FETUSES AND INFANTS WITHOUT SIGNIFICANT ASPIRATION OF AMNIOTIC SAC CONTENTS
Total number of patients	76	28	48
Patients with bronchopneumonia	20	14	6
Patients without bronchopneumonia	56	14	42

*Infants suffering from an intrapulmonary hyaline membrane were excluded since evidence has been presented both for and against the fact that this membrane may represent the contents of the amniotic sac. Bronchopneumonia occurred in only one of the fifteen infants with an intrapulmonary hyaline membrane who died within 24 hours after delivery; it was present in five of the six infants with an intrapulmonary hyaline membrane who died later than 24 hours after delivery.

should be considered a potential example of bronchopneumonia.

Summary.—Bronchopneumonia was present in 40 per cent of the liveborn infants in whom there was no evidence of congenital syphilis and in three of thirty-four nonsyphilitic fetuses. It was thought to represent the primary cause of death in ten liveborn infants. The majority of infants with bronchopneumonia who die within the first 24 hours after delivery have developed the process in utero. Intrauterine pneumonia is usually bronchogenic in origin, secondary to aspiration of contents of the amniotic sac. Although there is evidence to support the view that some examples of intrauterine pneumonia are due to the inhalation of sterile but irritating contents of the amniotic sac, many examples of intrauterine pneumonia are probably due to the aspiration of amniotic fluid which has been contaminated by bacteria. In the present series there was a significant increase in the incidence of intrauterine pneumonia following prolonged labor, or following excessive aspiration of amniotic debris. The diagnosis of bronchopneumonia in fetuses and infants dying shortly after delivery is dependent upon histologic examination of the lungs; the diagnosis cannot be established by gross examination alone.

CONGENITAL SYPHILIS

Congenital syphilis was responsible for nine fetal and neonatal deaths. Five additional infants had gross and/or microscopic findings which were probably the result of congenital syphilis, but in these a positive diagnosis could not be established. The latter are, therefore, considered to be examples of probable congenital syphilis and will be discussed separately. Stains for spirochetes were prepared from all five patients in the latter group in whom the histologic changes were insufficient to warrant a definite diagnosis of congenital syphilis. They were not prepared in the majority of patients in the former group, since it was felt that the gross and microscopic findings alone were sufficient to justify a positive diagnosis of congenital syphilis.

Among the nine fetuses and infants dying as a result of congenital syphilis there were eight liveborn premature infants and one stillborn full-term fetus. All of the members of this group were Negro. There were five males and four females. Their weights varied from 1,090 to 2,920 grams, with an average weight of 1,766 grams. The duration of life of the liveborn infants varied from 55 minutes to 6 days; six infants died less than 12 hours after delivery. The maternal serologic reaction of the blood was positive in eight cases; in the ninth no record of the maternal serologic reaction was available, but this mother was said to have received irregular antisyphilitic therapy during the last trimester of her pregnancy. The diagnosis of congenital syphilis was suggested during the life of six of the eight liveborn infants.

Splenomegaly was constantly present in the patients who died as a result of congenital syphilis, the weight of the spleen varying from 1.5 to over ten times the normal weight; in five of these infants the spleen weighed more than four times the expected normal weight. (The normal weight of the organ, based on the weight of the infant or fetus, was obtained from

the figures given by Potter and Adair.[84]) Occasionally, no gross abnormalities were noted in the spleen other than increased size. More frequently, however, patchy areas of thickened opaque capsule were noted, and at times fibrinous or fibrous adhesions were present between the spleen and the diaphragm, stomach, or liver. On section the splenic parenchyma was firm, but an increased amount of connective tissue was not demonstrable macroscopically. Although splenomegaly in congenital syphilis is often attributed to simple hyperplasia, in the present series the most constant histologic finding was that of extensive diffuse hematopoiesis, the hematopoietic cells often being of the large immature type seen in the viscera of patients dying of erythroblastosis fetalis. In addition, focal areas of necrosis were occasionally present, and were sometimes accompanied by areas of fibrosis and calcification. In one fetus the areas of necrosis suggested actual infarcts.

The weight of the liver varied from 1.1 to 2.0 times the normal weight; in six infants it was 1.5 times the normal weight or larger; in the remaining three patients the weight of the liver was probably within the range of normal variation. Multiple punctate gray zones were often visible beneath Glisson's capsule. The organ was often faintly green in the fresh state and deep green following fixation in formalin. Solitary yellow indurated areas 0.6 and 2.5 cm. in diameter were present on the surface of the liver in two infants; otherwise, no definite increase of connective tissue was demonstrable grossly. Histologically diffuse hematopoiesis similar to that noted in the spleen was usually present. The portal connective tissue often contained a rather heavy infiltrate of myelopoietic cells. Atrophy and disappearance of hepatic cords with collapse of the stroma was encountered more frequently than actual increase of intralobular connective tissue. In the solitary foci of induration noted macroscopically, however, the hepatic architecture was almost entirely destroyed by a diffuse fibrotic process; multiple miliary abscesses were present throughout one such focus. Such solitary nodules occurring in the viscera of patients with congenital syphilis have often been erroneously referred to as gummas.[41]

Definite pancreatic changes were demonstrable in six infants. Two infants revealed no distinct gross or microscopic alterations in the pancreas. The pancreas of the stillborn fetus contained a rather heavy infiltrate of lymphocytes about the larger ducts but was otherwise not remarkable. The most constant finding in the pancreas was that of a diffuse interstitial fibrosis with a paucity of acini but with little or no involvement of the islets of Langerhans. Diffuse or focal infiltrates of macrophages, lymphocytes, neutrophils, and hematopoietic cells were often associated with the interstitial pancreatic fibrosis, and in one infant large areas of necrosis and calcification were present.

Among the most constant pathologic findings in patients with congenital syphilis are those occurring in the ends of the long bones.[96] Gross or microscopic abnormalities at the line of ossification were noted in all of the patients in this series, although they varied considerably in intensity from case to case and even in different

bones in any one case. In some instances the line of ossification appeared relatively straight but was wide and yellow. In others an increased width and a yellow discoloration of the line of ossification were associated with varying degrees of irregularity, culminating in the classical "saw-tooth" line of ossification. A distinct yellow discoloration of the marrow itself was noted in a few instances.

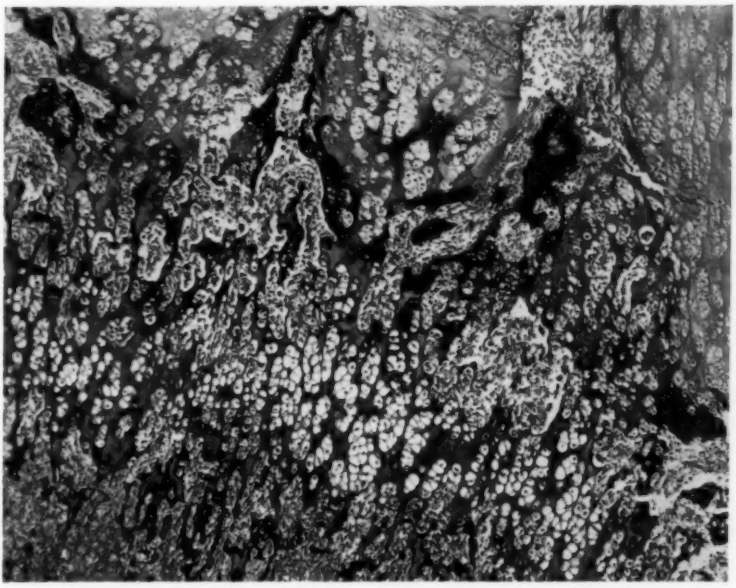

Fig. 7.—Section of the epiphyseal line of the upper end of the tibia illustrating syphilitic osteochondritis. The zone of provisional calcafication is wide and irregular, the zone of "hypertrophic" cartilage cells is wide, and there is irregular penetration of capillaries into the cartilage. (×35.)

Histologically the less severely involved bones revealed only an increased zone of large, clear, degenerating cartilage cells, an abnormally wide zone of provisional calcification, and varying degrees of irregularity of the line of ossification; little or no inflammatory infiltrate was present at the line of ossification. In the more severely involved cases, however, there was severe distortion of the line of ossification with irregular vascularization of the cartilage, persistence of cartilage matrix and cells well into the metaphysis, and separation of cartilaginous and bony trabecula by cellular connective tissue (Fig. 7). Fibrosis of the marrow with loss of normal hematopoietic activity was occasionally present, as was a reactive or exudative periostitis.

Excellent descriptions of the osseous changes of congenital syphilis are included in the papers of Wegner,[118] Schmidt,[96] Tschistowitsch,[112] and Schneider.[98] Wegner differentiated three stages of osteochondritis. The first stage is characterized by a slightly increased growth of the cartilage cells, a widened zone of pro-

visional calcification of cartilage, and a retardation in the transformation of cartilage into true bone. The second stage is essentially a progression of stage one with a still wider zone of calcified cartilage and extreme irregularity of the zone of provisional calcification, the latter extending as irregular warty processes of calcified cartilage far into the epiphyseal cartilage. The third stage is characterized by a progression of the changes noted in the preceding stages, but now the additional feature of a zone of granulation tissue and inflammatory infiltrate is present in the region of the metaphysis. In this stage separation of the epiphysis may occur as a result of the destruction of cartilage and bone and their replacement by this zone of granulation tissue. According to Wegner the various stages of syphilitic osteochondritis are essentially a progression of one another, the granulation tissue of stage 3 merely representing reaction to necrosis brought about by impaired nutrition of the heavily calcified cartilage. Schneider,[98, 99] however, divides syphilitic osteochondritis into a passive form (Wegner's stages 1 and 2) and an active form (Wegner's stage 3) and feels that these two forms may represent different types of reaction rather than successive stages of one another, active osteochondritis representing more vigorous reaction on the part of the host to the spirochetes.

Although no classical examples of pneumonia alba were seen macroscopically in this series, pulmonary changes which were presumably the result of congenital syphilis were demonstrable in six of the nine fetuses and infants. The most frequent finding was that of an interstitial pneumonitis, the alveolar septa being thickened by a cellular infiltrate of mononuclear cells. Less frequently numerous large mononuclear cells were present in the pulmonary alveoli and in the pleura. Both these histologic patterns have been described as "pneumonia alba."

In addition to these changes which were presumably specific in character, six patients had focal accumulations of neutrophils in the alveoli, i.e., an apparently nonspecific bronchopneumonia. Similar findings have been reported by Chase,[24] who attributes the death of the majority of syphilitic infants under one month of age to aspiration pneumonia following intrauterine asphyxia.

Gross evidence of meningitis was not demonstrable in these patients with congenital syphilis, although the basilar meninges sometimes appeared slightly opaque and the subarachnoid fluid somewhat gelatinous and increased in amount. Histologic sections of the brain and meninges were available for study in all but one patient. In four there was a subacute or chronic meningitis consisting of an infiltrate of macrophages in the leptomeninges, occasionally with an associated lymphocytic infiltrate.

Gross evidence of syphilitic enteritis in the form of raised yellow bands encircling the ileum, as described by D'Aunoy and Pearson,[30] was not encountered in the present series. However, histologic sections of the bowel, available in eight patients, revealed a definite inflammatory infiltrate in four. The lamina propria was often relatively acellular; rarely, it contained an infiltrate of lymphocytes, plasma cells, macrophages, and neutrophils.

The submucosa was fibrotic and contained an infiltrate of similar cells; in one patient there was perivascular proliferation of fibroblasts with resultant formation of multiple concentric rings of collagen about the submucosal vessels. The muscularis contained a cellular exudate consisting principally of neutrophils with varying numbers of lymphocytes; the neutrophilic infiltrate was often focal as well as diffuse, forming minute miliary abscesses in or between the muscle coats. Varying degrees of inflammatory infiltrate were present in the serosa; in one patient fibrous adhesions had occurred between two adjoining loops of jejunum. These changes in the bowel were often associated with a diffuse increase of macrophages in the mesenteric lymph nodes.

Histologic sections of the hypophysis were available in five patients; in two there was definite evidence of syphilitic hypophysitis.[97] The hypophysis in these two patients was yellow and protruded well above the sella turcica. Histologically there was diffuse interstitial fibrosis of the anterior lobe of the hypophysis; in one there also were miliary foci of necrosis. Steiner[108] has attributed such miliary necroses in congenital syphilis to conglomerations of actively reproducing spirochetes.

Sections of the adrenal glands were available in eight of the nine patients. In three patients there was an infiltrate of macrophages in the capsule of the adrenal and in the adjoining connective tissue. In one of these patients and in one additional patient capsular extensions of connective tissue were present in the superficial cortex, separating the cells of the latter. According to Fite,[48] such capsular changes are the most frequent characteristic lesion in the adrenal glands of patients with congenital syphilis; nevertheless they were observed by him in less than 10 per cent of the cases of congenital syphilis. This rarity of pathologic alteration in the structure of the adrenal glands in congenital syphilis is in striking contrast to the frequency with which spirochetes can be demonstrated in these glands; they are one of the most frequent sites in which spirochetes can be demonstrated in cases of congenital syphilis.[48, 110]

There were five additional liveborn infants in whom the pathologic findings suggested the diagnosis of congenital syphilis but were insufficient to establish this diagnosis positively. Three of these infants are included in the group of cases in which no anatomic cause of death was demonstrated; one infant died as a result of fetal anoxia and one as a result of a purulent meningitis. The maternal serologic reaction of the blood was recorded as positive for three of these infants; in two no record of the maternal serologic reaction was available. Three mothers gave a history of receiving antisyphilitic therapy during pregnancy, but the time, type, and amount of therapy were not always stated.

The pathologic changes which suggested the possibility of congenital syphilis in these patients were principally osseous. However, inasmuch as four of the five infants were premature and lived 7 to 21 days, the possibility that the osseous changes were due to vitamin deficiencies rather than to congenital syphilis could not be excluded. Large immature hema-

topoietic cells were present in extramedullary foci in two patients, but such a change is nonspecific and does not warrant a positive diagnosis of congenital syphilis. In one infant there was a suggestion of focal intralobular hepatic fibrosis, but the appearance of the hepatic lesions was not entirely typical of those seen in congenital syphilis and no spirochetes could be demonstrated in the liver. Stains for *Treponema pallidum* were uniformly negative in all five patients in this latter group.

Summary.—Congenital syphilis was responsible for nine fetal and neonatal deaths. All but one of the patients in this group were liveborn premature infants. Splenomegaly, syphilitic osteochondritis, and extramedullary hematopoiesis were the most constant abnormalities, followed by syphilitic pancreatitis, moderate hepatomegaly, and syphilitic inflammation of the lungs. Other less frequent findings included syphilitic involvement of the leptomeninges, bowel, adrenals, and hypophysis. In addition to these nine patients there were five infants with findings which suggested the diagnosis of congenital syphilis, but in whom this diagnosis could not be established positively either by the histologic changes or by stains for spirochetes.

INTRACRANIAL TRAUMA

Intracranial trauma as manifested by tears of the dural septa with or without subdural hemorrhage was considered responsible for seven fetal and neonatal deaths. There were three stillborn fetuses and four liveborn infants; the duration of life in the latter group varied from 1 hour 12 minutes to 5 hours 35 minutes. Four patients were full term and three were premature. Their weights at the time of autopsy varied from 850 to 3,440 grams; their average weight was 2,552 grams. Five patients were Negro and two were white; there were six males and one female.

The dural tears involved only one leaf of the tentorium cerebelli in three patients, the falx cerebri alone in two patients, and both leaves of the tentorium cerebelli and the falx cerebri in two patients. Significant amounts of subdural hemorrhage were present in five patients. In one of the other two patients, a premature fetus weighing 1,660 grams, only a small amount of subdural hemorrhage was present in association with a tear of the falx cerebri. In the other patient, a premature infant weighing 850 grams, there was no subdural hemorrhage in spite of bilateral tentorial tears and a tear of the falx cerebri.

Dural tears were present in an additional seven stillborn fetuses and in two liveborn infants. In these nine patients intracranial trauma was not thought to be the primary cause of death, and in none of this latter group were there significant amounts of subdural hemorrhage.

In the entire series of sixteen patients the dural tears involved only one leaf of the tentorium cerebelli in ten patients; bilateral tentorial tears were present in four. Tears of the falx cerebri were present in four patients; in two of this latter group there were associated bilateral tentorial tears.

The tentorial tears involved only the superficial fibers of the tentorium cerebelli in eleven patients; complete tears involving both superficial and

deep fibers were present in three. In the complete tears the free anterior edge of the tentorium cerebelli was involved in the tear, whereas in the superficial tears the free edge of the tentorium was usually intact. The tentorial tears were usually located at or near the junction of the fibers of the falx cerebri and tentorium cerebelli; those in the falx cerebri were located in the middle or posterior one-third of the falx. As noted above, significant amounts of subdural hemorrhage were confined to those patients in whom intracranial trauma was considered to be the primary cause of death, but even in this group significant amounts of subdural hemorrhage were absent in two patients.

Dural tears are produced by excessive or by too rapid molding of the head, with resultant overstretching and tearing of the fibers of the tentorium cerebelli, or less frequently of the falx cerebri. Abnormal elongation of any diameter of the skull may produce such tears, but vertical elongation appears to be particularly dangerous.[51] According to Holland,[58] compression of the head in the suboccipitobregmatic diameter results in vertical elongation of the skull. Greenwood,[51] however, believes that engagement of the suboccipitobregmatic circumference, as occurs in the majority of vertex presentations, results in an anteroposterior elongation with no increase in the vertical diameter of the skull; on the contrary, the forces acting on the aftercoming head of a breech presentation result in an increase in the vertical diameter of the skull. Regardless of this discrepancy of opinion, it is generally agreed that tentorial tears are especially likely to occur in fetuses and infants delivered as breech presentations in contrast to those delivered as vertex presentations. In the present group of sixteen patients there were five delivered as breech presentations, nine as vertex presentations with the occiput directed anteriorly, one as a vertex presentation with the occiput directed posteriorly, and one fetus was delivered by cesarean section. The presentation of 130 of the entire 137 fetuses and infants is recorded as follows: eighty-seven were delivered as vertex presentations, twenty-eight were delivered as breech, fourteen were delivered by cesarean section, and one abdominal pregnancy was delivered by laparotomy. Thus, in the present series five of the twenty-eight fetuses and infants delivered as breech presentations had dural tears (17 per cent), as compared to ten of the eighty-seven fetuses and infants delivered as vertex presentations (11 per cent). This difference is not statistically significant.

The fact should be emphasized that tears of the dural septa per se are of little or no clinical significance and are not themselves lethal lesions. Hemorrhage resulting directly from tears of the dural septa is usually slight or absent[58]; extensive subdural hemorrhage associated with tentorial tears is usually secondary to stretching and tearing of the tributaries of the great cerebral vein.[23, 57] There is no absolute relationship between the degree of tentorial damage and the amount of subdural hemorrhage.[23] It seems highly probable that many dural tears heal spontaneously without producing symptoms. On the other hand, dural tears are definite evidence of abnormal intracranial stress and as such may be a mani-

festation of the cause of death. The subdural hemorrhage which may accompany dural tears is the usual lethal lesion.

Summary.—Intracranial trauma, as manifested by tears of the dural septa with or without subdural hemorrhage, was responsible for seven fetal and neonatal deaths. Significant amounts of subdural hemorrhage were present in five of these seven patients; in two premature patients, however, the abnormal intracranial stress responsible for the dural tears was considered to be responsible for death, even though significant amounts of subdural hemorrhage were absent.

Tears of the dural septa were present in nine additional fetuses and infants; in this latter group they were not associated with significant amounts of subdural hemorrhage and were not thought to represent the primary cause of death.

There was no significant increase in the incidence of tears of the dural septa in fetuses and infants delivered as breech presentations when compared to fetuses and infants delivered as vertex presentations.

Tears of the dural septa are definite evidence of abnormal intracranial stress, but the tears themselves are not lethal lesions. It seems highly probable that many dural tears may heal spontaneously and give rise to no symptoms. The subdural hemorrhage which may accompany these tears is the usual cause of death.

MISCELLANEOUS LESIONS

Miscellaneous lesions accounted for the deaths of eighteen infants in the present series. These included examples of kernicterus (five), dural sinus thrombosis (two), meningitis (two), erythroblastosis fetalis (two), bilateral tension pneumothorax (two), and one example each of massive intrapulmonary hemorrhage, severe subarachnoid hemorrhage, omphalitis, infarction of the brain, and sepsis. All of the patients in this group were liveborn infants. Details with respect to age, weight, sex, and race are recorded in Table VIII.

Comment should be made concerning the patients with kernicterus. In five infants death was attributed to kernicterus. In all of these infants the immediate cause of death was probably pulmonary in nature, as evidenced by severe intrapulmonary hemorrhage or pulmonary edema. However, since such pulmonary changes may be secondary to damage to the central nervous system, manifested grossly by kernicterus, the latter was arbitrarily considered the primary cause of death. Kernicterus was present in an additional four Negro infants in whom it was not considered to be the primary cause of death.

Gross or microscopic abnormalities sufficient to warrant a diagnosis of erythroblastosis fetalis were present in only one of these nine infants with kernicterus. Since serologic studies of the blood groups and Rh types of the mothers and infants were not performed routinely the diagnosis of erythroblastosis fetalis could not be excluded positively in the remaining eight infants. It is recognized that histologic changes may be minimal in the organs of some infants dying with kernicterus, and the diagnosis of hemolytic disease in such infants may be difficult or impossible to establish on the basis of purely morphologic studies.[82] Furthermore, although erythroblastosis fetalis has been con-

sidered to be rare among Negroes,[120] evidence has recently been presented to indicate that isosensitization occurs in Rh_o-negative American Negroes with approximately the same frequency as in Rh_o-negative Caucasoid individuals; therefore, since the incidence of the Rh-negative type in the American Negro is only slightly more than one-half of that in Caucasians, the incidence of erythroblastosis fetalis in Negroes should be correspondingly lower.[94]

whom the diagnosis of erythroblastosis fetalis and other forms of isoimmunization was excluded by serologic studies of the mothers and infants.

DEATH FROM UNKNOWN CAUSES

There were thirty fetuses and infants in whom no anatomic cause of death could be demonstrated. Fifteen were stillborn fetuses and fifteen were liveborn infants. The duration of life of the liveborn infants varied from 5 minutes to 21 days; eleven infants lived less than 3 hours. The

TABLE VIII. MISCELLANEOUS CAUSES OF DEATH

AGE	WEIGHT IN GRAMS AT TIME OF AUTOPSY	SEX	RACE	CAUSE OF DEATH
3 da.	2,300	Male	Negro	Kernicterus
6 da.	1,940	Female	Negro	Kernicterus
8 da.	1,400	Female	Negro	Kernicterus
5 da.	1,200	Male	Negro	Kernicterus
5 da.	2,000	Male	White	Kernicterus
14 da.	1,520	Male	Negro	Thromboses of dural sinuses
19 da.	1,128	Female	Negro	Thromboses of dural sinuses
7 da.	1,065	Male	Negro	Meningitis
11 da.	1,700	Male	Negro	Meningitis, localized
7 da.	2,240	Male	Negro	Erythroblastosis fetalis
2 hr.	3,030	Female	Negro	Erythroblastosis fetalis
3 hr.	1,820	Male	Negro	Bilateral tension pneumothorax
37 min.	1,680	Male	Negro	Bilateral tension pneumothorax
1 da.	900	Male	Negro	Intrapulmonary hemorrhage
31 min.	520	Female	White	Severe subarachnoid hemorrhage
2 da.	1,550	Male	Negro	Infarction of brain
11 da.	1,410	Male	Negro	Omphalitis
15 da.	1,200	Female	Negro	Sepsis

The facts mentioned above cast some doubt on the absence of erythroblastosis fetalis in these infants. However, the paucity of clinical and pathologic evidence of erythroblastosis fetalis and the fact that eight of the nine infants were Negro suggest that some of these infants may represent examples of kernicterus occurring in nonerythroblastotic infants. Although this supposition could not be proved in this series, Zuelzer and Mudgett[129] have recently reported a considerable series of patients with kernicterus in

weights of the liveborn infants at the time of autopsy varied from 640 to 3,580 grams; their average weight was 1,575 grams. Only two of these infants were full term as judged by weight, and six were previable premature infants. The weights of the stillborn fetuses varied from 840 to 3,200 grams; their average weight was 2,234 grams. In the entire group of thirty fetuses and infants there were nineteen females and eleven males. Twenty-two patients were Negro and eight were white.

The manner of delivery was recorded for twenty-eight fetuses and infants. Twelve patients were delivered as vertex presentations, ten as breech presentations (including one version and extraction), and six were delivered by cesarean section.

More complete maternal records were available for twenty-five of the fetuses and infants in this group. There were five examples of premature separation of the placenta, two of placenta previa associated with the loss of significant amounts of blood prior to delivery, and one example each of prolapse of the umbilical cord and of spontaneous rupture of the uterus following prolonged labor. All of the fetuses and infants for whom the above complications were recorded were either stillborn or died within 2 hours after delivery. Thus, in at least one-third of the fetuses and infants for whom maternal records were available and in whom no anatomic cause of death could be demonstrated, the maternal records suggested intrauterine anoxia as the cause of death.

DISCUSSION

Although fetal and neonatal deaths account for more than 150,000 deaths per year in the United States, or more than two-thirds the number of deaths attributed to cancer during the same period, investigation of the causes of death of these fetuses and infants is often cursory and is unsatisfactory from the standpoint of both the clinician and the pathologist. The cause of death is frequently attributed to prematurity alone; however, this is never a cause of intrauterine death and by itself is rarely adequate to explain the death of a liveborn infant. In like manner atelectasis, to which the cause of death is often assigned, is not a cause of intrauterine death and should not be considered as a primary cause of extrauterine death. Unqualified diagnoses such as these, often based on incomplete post-mortem examinations and inadequate clinical records, add little or nothing to the knowledge of the clinician interested in determining the cause of death of a given patient. Furthermore, the erroneous assumption that such diagnoses are adequate to explain the death of a fetus or infant leads to apathy on the part of the pathologist, who may feel that prematurity and atelectasis explain the majority of fetal and neonatal deaths and that little is to be gained by detailed post-mortem examinations. It is no wonder, then, that clinicians and pathologists alike frequently consider necropsies on fetuses and infants to be of little value and accordingly relegate the performance of such necropsies to the inexperienced pathologist.

The lack of cooperation between clinicians and pathologists dealing with newborn infants is particularly unfortunate, since there is probably no period of life during which clinical diagnoses are so unreliable. The responses of the newborn infant to a variety of stimuli, anoxic, traumatic, or infectious, are relatively limited, and as a result, a variety of pathologic processes may produce similar clinical signs and symptoms. The true nature of the underlying disease can often be established only by means of a detailed post-mortem examination.

Not only must the clinician have the cooperation of the pathologist in

order to determine the true cause of death, but the pathologist must avail himself of all of the clinical data in order to interpret correctly the findings at the post-mortem examination. For example, in the absence of any maternal record it may be impossible to evaluate the relative importance of a superficial tear of one leaf of the tentorium cerebelli, mild subdural hemorrhage, and moderately severe aspiration of amniotic debris in an infant dying two hours after birth. To continue this hypothetical case, however, the maternal record might reveal the loss of large amounts of blood secondary to an abruptio placentae, a decline in the fetal heart rate occurring shortly after the onset of labor and coincident with the hemorrhage, and a slow fetal heart rate persisting throughout the course of labor. In view of these clinical and pathologic observations it would seem logical to assume that intrauterine anoxia, as evidenced by the aspiration of excessive amounts of amniotic debris was the primary cause of death, with intracranial trauma a contributory factor. Obviously, in many cases only an arbitrary decision can be made as to the primary cause of death, but such decisions can be made more intelligently when the pathologic findings are correlated with the clinical record of the mother and infant.

As has been pointed out, prematurity is never an adequate explanation for intrauterine death and only rarely, in extreme instances, may prematurity alone explain an extrauterine death. However, the importance of prematurity as a factor in neonatal deaths can hardly be overemphasized. Premature infants comprise only 5 to 10 per cent of all livebirths; nevertheless, well over 50 per cent of all neonatal deaths occur in premature infants. Furthermore, the mortality rates of premature infants are inversely proportional to their birth weights. In spite of the close association of prematurity with neonatal mortality, careful post-mortem examinations will reveal, in addition to immaturity, a cause of death in the majority of premature infants. In the present series, for example, an adequate cause of death was demonstrated in seventy-one of the eighty-four premature liveborn infants (84 per cent). Acceptance of the fact that prematurity, uncomplicated by other disorders, is seldom the sole cause of death should result in more adequate prevention, diagnosis, and treatment of such disorders. This in turn should cause a decrease in the neonatal mortality rate of premature infants.

Statistical surveys of the causes of death of large numbers of fetuses and infants, based on post-mortem examinations, have been presented by a number of authors.[28, 33, 64, 70, 85] However, certain features noted in the present series are worthy of further comment, i.e., (1) the high incidence of inflammatory lesions, and (2) the frequency of pulmonary lesions.

Inflammatory lesions (bronchopneumonia, congenital syphilis, meningitis, omphalitis, and sepsis) were considered responsible for twenty-three of the 137 fetal and neonatal deaths (16 per cent); they were considered responsible for the deaths of twenty-two of the 102 liveborn infants (21 per cent), and for only one of the thirty-five fetal deaths. Among the twenty-two infants dying as a result

of inflammatory conditions, eleven lived less than 24 hours.

Inflammatory processes of various types were present in an additional thirty-two infants and five fetuses in whom the primary cause of death was not considered to be inflammatory in nature; included in this group were examples of bronchopneumonia, otitis media, omphalitis, meningitis, and peritonitis. Although a few of the inflammatory conditions in these patients were directly related to the primary cause of death (as inflammation of the meninges in association with anencephaly), more frequently no such definite relationship could be established.

Thus, in the entire series of 137 fetuses and infants inflammatory lesions were present as primary or contributory causes of death in sixty (43 per cent); they were present in fifty-four (52 per cent) of the live-born infants and in six of the thirty-five stillborn fetuses. Inflammatory lesions were present in twenty-six of the sixty-four infants who died less than 24 hours after delivery.

In some of these fetuses and infants the cellular infiltrate was so slight that it is doubtful if the inflammatory process played any significant part in the death of the patient. Furthermore, it is quite possible that some of the inflammatory lesions in fetuses and infants who died during the early neonatal period may have been noninfectious in origin. Evidence has already been presented to indicate that some examples of intratuerine bronchopneumonia may be due to the inhalation of sterile, but irritating, contents of the amniotic sac. However, recognition of these facts should detract little from the importance of infection as a primary or contributory cause of death during the neonatal period. Although bacteriologic proof is lacking in this series (because of the nature of the post-mortem material available), it seems highly probable that many, if not the majority, of the inflammatory processes described in these infants were due to infectious agents; those observed in infants who died several days after delivery were undoubtedly infectious in origin.

Signs and symptoms referable to infection are often obscure or absent in newborn infants, and as a result, the diagnosis of infection may not be suspected until post-mortem examination is performed. Accordingly, the clinician dealing with newborn infants must be cognizant of the frequency of infections during this period of life, so that the proper chemotherapeutic and antibiotic agents may be administered both prophylactically and therapeutically at an early stage.

The pathologist performing post-mortem examinations on fetuses and infants who die during the neonatal period should be aware of the conditions commonly responsible for the deaths of such patients. Careful gross examination of the contents of the cranial cavity and histologic examination of the lungs would have elicited the cause of death in over one-half of the fetuses and infants in this series, and histologic examination of the lungs alone would have indicated the cause of death in forty-nine fetuses and infants (35 per cent). Discussions of the lesions demonstrable in the lungs of these fetuses and infants have been included in the sections on intrauterine anoxia, intrapulmonary hya-

line membrane, and bronchopneumonia. In addition, there was one example of massive intrapulmonary hemorrhage; the exact etiology of this lesion is not clear, some authors favoring an infectious origin and others attributing the lesion to anoxia or to cerebral damage.

Although histologic examination of the lungs will frequently elicit the cause of death of fetuses and newborn infants, pulmonary lesions only can be interpreted properly when correlated with a complete post-mortem examination and clinical record. Furthermore, the fact should be emphasized that the pulmonary lesions demonstrable may not be directly responsible for death. For example, aspiration of excessive amounts of amniotic debris is indicative of intrauterine anoxia; it is the anoxia which is usually responsible for death rather than the presence of amniotic debris within the lungs. In such patients examination of the placenta or a careful maternal history may reveal the cause of the intrauterine anoxia.

The fact should be emphasized that gross examination of the lungs of fetuses and newborn infants is usually entirely unsatisfactory from the diagnostic standpoint, and that definitive diagnoses of pulmonary lesions can be established only by examination of histologic sections. Moreover, the lesions may not be distributed uniformly throughout both lungs, and their intensity may vary at different sites, so that multiple sections of the lungs must be examined histologically in order to evaluate properly the importance of any given lesion.

From a review of the discussions of the various pulmonary lesions encountered it should be obvious that the pathogenesis and significance of many of these lesions is only poorly or not at all understood. Only by means of carefully conducted experimental, clinical, and post-mortem studies, and correlation of the findings brought out by such studies can these problems be further elucidated. It is hoped that the present paper may serve as a stimulus to such studies.

SUMMARY

An adequate anatomic cause of death was demonstrated in 107 of 137 fetuses and infants who died during the neonatal period; anatomic causes of death were demonstrable in eighty-seven (85 per cent) of the 102 liveborn infants and in twenty of the thirty-five stillborn fetuses.

Intrauterine anoxia, as evidenced by aspiration of excessive amounts of the contents of the amniotic sac, was the single leading cause of death, accounting for 16 per cent of the fetal and neonatal deaths. From the available evidence, it is concluded that repeated deep intrauterine respiratory movements with resultant aspiration of large amounts of amniotic debris are not a normal occurrence and that the presence of large amounts of amniotic debris in the lungs is evidence of fetal anoxia. Fetuses and infants dying as a result of fetal anoxia probably do so as the result of cerebral damage and not primarily as a result of the inhalation of amniotic debris.

Intrapulmonary hyaline membranes were the leading cause of death in liveborn infants, accounting for the deaths of fifteen premature infants; such membranes were not observed in stillborn fetuses. The pathogenesis of these intrapulmonary hyaline mem-

branes is discussed. Although no conclusions are reached as to the nature of the material comprising the membranes, evidence is advanced to support the concept that vascular damage and increased capillary fragility may play a role in their origin.

Major congenital anomalies were responsible for the deaths of fourteen fetuses and infants, and major or potentially lethal anomalies were present in three other patients. More than one anomaly was present in over 50 per cent of those fetuses and infants whose deaths were attributed to congenital anomalies. Minor congenital anomalies, some of which might assume clinical significance somewhat later in life, were often present in the absence of any major anomaly.

Intraventricular hemorrhage was the single leading cause of death of previable premature liveborn infants. Although other factors play a part in their pathogenesis, prematurity is certainly the most important factor predisposing to intraventricular hemorrhage.

Bronchopneumonia was considered responsible for the deaths of ten liveborn infants and was present in twenty-nine other nonsyphilitic fetuses and infants. Although some examples of intrauterine pneumonia may be secondary to aspiration of sterile, but irritating, contents of the amniotic sac, many are probably due to the aspiration of amniotic fluid which has been contaminated by bacteria. There was a significant increase in the incidence of pneumonia, presumably developing in utero, following prolonged labor or aspiration of excessive amounts of amniotic debris.

Congenital syphilis was responsible for nine fetal and neonatal deaths. Splenomegaly, syphilitic osteochondritis, and extramedullary hematopoiesis were the most constant abnormalities found in these patients, followed by syphilitic pancreatitis, moderate hepatomegaly, and syphilitic inflammation of the lungs. Other less frequent findings included syphilitic involvement of the leptomeninges, bowel, adrenals, and hypophysis.

Intracranial trauma, as manifested by tears of the dural septa with or without subdural hemorrhage, was responsible for seven fetal and neonatal deaths. Many tears of the dural septa probably heal spontaneously and give rise to no definite symptoms; the subdural hemorrhage which may accompany dural tears is the usual cause of death.

Kernicterus was considered to be the primary cause of death in five liveborn infants and was present as a contributory cause in four other infants. The available evidence suggests that some of these infants represent examples of kernicterus occurring in nonerythroblastotic infants.

In at least one-third of the fetuses and infants for whom maternal records were available and in whom no anatomic cause of death could be demonstrated, the maternal records suggested intrauterine anoxia as the cause of death.

Prematurity, uncomplicated by other disorders, is seldom the sole cause of death. Careful post-mortem examinations will reveal, in addition to immaturity, a cause of death in the majority of premature infants dying during the neonatal period.

Inflammatory lesions, many of which are probably infectious in ori-

gin, play an important role as primary and contributory causes of death in the neonatal period; they were present in 52 per cent of the liveborn infants in this series.

Histologic examination of multiple sections of the lungs is an essential part of any post-mortem examination of a fetus or newborn infant. In this series, histologic examination of the lungs alone would have indicated the cause of death in 35 per cent of the fetuses and infants. The pulmonary lesions encountered are frequently indicative of the cause of death, but can be interpreted properly only when correlated with the clinical record and with the findings of a complete post-mortem examination. Further studies are necessary for a better understanding of the pathogenesis and significance of many of the commonly observed pulmonary lesions.

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TREATMENT OF OBSTRUCTIVE ATELECTASIS BY AEROSOL ADMINISTRATION OF PROTEOLYTIC ENZYMES

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AEROSOL administration of bronchodilating drugs, such as epinephrine and Neo-Synephrine, has proved helpful in the management of postoperative atelectasis.[1]

In the following case of obstructive atelectasis, the proteolytic enzymes streptokinase (SK), streptodornase (SD), and crystalline trypsin were employed in a similar manner in an attempt to dissolve the exudative plug blocking the bronchus.

The patient thus treated suffers from amyotonia congenita and has marked weakness of the intercostal muscles. Bronchoscopic aspiration under general anesthesia was postponed because of its obvious risk. In view of the poor prognosis, the rapid recovery following the use of aerosol trypsin prompted this report.

CASE REPORT

M. E., white male, 4 years of age, was admitted to Southern Baptist Hospital, New Orleans, La., on April 9, 1952, with a high temperature and chest pain of twelve hours' duration. For three weeks prior to admission, the patient had been under treatment for an upper respiratory infection which persisted despite prolonged treatment with penicillin and terramycin.

The diagnosis of amyotonia congenita was made when the patient was 10 months old. The lower extremities have been flaccid from birth but recently there has been slight increase in the muscle tone of the upper extremities and back. The patient has never been able to sit without support and feeds himself poorly. He recovered from two attacks of pneumonia in the second year of life.

Physical examination revealed an acutely ill child with marked respiratory distress. He was moderately dehydrated and had an oral temperature of 103° F. The P.M.I. was displaced to the left anterior axillary line and the trachea was displaced 1 cm. to the left at the suprasternal notch.

Dullness and tubular breath sounds were noted at the left base. Breathing was largely diaphragmatic and the child was unable to cough up the loose mucus in the tracheobronchial tree.

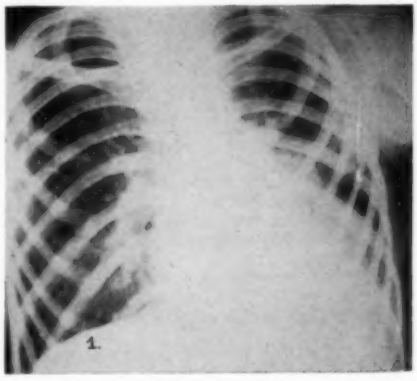

Fig. 1.—Anteroposterior view, April 11, 1952, showing atelectasis of left lower lobe and bilateral interstitial pneumonia.

There was complete paralysis of the lower extremities and marked weakness of the upper extremities.

Laboratory studies were as follows: x-ray of chest revealed atelectasis of left lower lobe and bilateral interstitial pneumonia (Fig. 1). The white blood count was 18,500 with 68 per cent neutrophils, 30 per cent lymphocytes, and 2 per cent eosinophils. From the pharynx cultures of *Pseudomonas aeruginosa* and alpha hemolytic streptococci were obtained. There was a 3 plus acetonuria.

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Course in the Hospital.—The temperature fell and the patient looked brighter following hydration and institution of penicillin, streptomycin, and chloramphenicol therapy. Moist oxygen had been given from admission, but the dyspnea persisted and the physical findings in the chest remained unchanged. The patient was unable to cough forcibly and was too weak to breathe deeply or inflate balloons.

Bronchoscopic aspiration was withheld because of the dangers of general anesthesia in amyotonia congenita.

On the fourth hospital day, a preparation of streptokinase (SK) and streptodornase (SD)* was given by the aerosol route as follows: SK 100,000 units and SD 25,000 units were dissolved in 12 c.c. of normal saline. Using a No. 40 De Vilbiss nebulizer attached to an oxygen cylinder, 3 c.c. of this solution was nebulized at thirty-minute intervals and inhaled by the patient through a mask. Nebulization of 3 c.c. required about ten minutes. Although some improvement was noted the following day, the physical signs and chest plate (Fig. 2) showed persistence of atelectasis.

*Varidase, Streptokinase-Streptodornase, Lederle Laboratories, New York.

On April 14, the sixth hospital day, Dr. John Dent of the Department of Pediatrics of Tulane University suggested that the more potent mucolytic enzyme trypsin might be preferable to SK-SD in this case. Crystalline trypsin 250 mg. was dissolved in 12 c.c. of Sorensen's phosphate buffer solution and 3 c.c. was nebulized every thirty minutes for four doses. Another 250 mg. of trypsin was inhaled in the same manner later that night. Following this course, rapid expansion of the collapsed lobe occurred within a few hours, as evidenced by physical findings and roentgenograms (Fig. 3). Moist râles over the involved area gradually disappeared during the next two days and the patient was discharged from the hospital. Antibiotics were continued at home until recovery was complete.

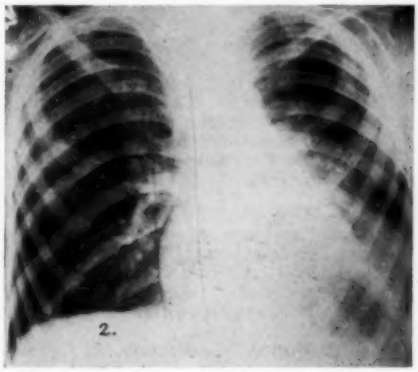

Fig. 2.—Anteroposterior view, April 14, 1952, showing little change following five days of treatment.

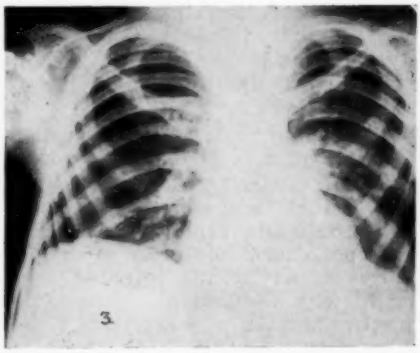

Fig. 3.—Anteroposterior view, April 16, 1952, the day following aerosol trypsin, showing marked clearing of left lower lobe.

DISCUSSION

The proteolytic enzymes used above are now being employed in a wide range of diseases.

Streptokinase and streptodornase[2] are elaborated by hemolytic streptococci, Group C. The former is chiefly fibrinolytic and the latter reduces the viscosity of pus by splitting the nucleoproteins of this exudate. These

enzymes have been used in such varied conditions as chronic osteomyelitis, burns, ulcers, empyema, hemothorax, tuberculous meningitis[3] and, in general, wherever the removal of fibropurulent exudate is desirable. The preparation has been used locally, intrapleurally, and intrathecally.

Crystalline trypsin* is a highly purified extract from mammalian pancreas glands. It acts on a wide variety of proteins and can be used whenever necrotic tissue is present. Like SK-SD, it has been found useful in the treatment of chronic suppurations and has been used locally and intrapleurally. Trypsin is a more effective mucolytic while SK is a more potent fibrinolytic.

Pyrogenic reactions have not been observed from trypsin and are rare with SK-SD. However, the possibility of histamine-like reactions can be minimized by the concomitant use of antihistaminics.

The aerosol route of administration of these enzymes would seem to have certain limitations.[4] The main objection is that these enzymes are labile and deteriorate rapidly in solution. It is not known how much of the potency is lost by the agitation associated with nebulization. Second, the preparations are still expensive.

Bronchoscopy is the most direct approach to the problem of obstructive atelectasis. Even here, however, the intrabronchial instillation of trypsin or SK-SD might prove a useful adjunct in the lysis of mucus or purulent exudate not completely removable by suction.

*Crystalline trypsin (Tryptar), Armour Laboratories, Chicago, Ill.

SUMMARY

A patient with obstructive atelectasis in whom bronchoscopic aspiration was considered hazardous recovered dramatically following the aerosol administration of crystalline trypsin. It is felt that the use of trypsin or streptokinase and streptodornase by this route merits further trial. The suggestion is made that the intrabronchial instillation of the appropriate proteolytic enzyme in conjunction with suction might result in more complete removal of the blocking exudate.

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DEFICIENT PROTHROMBIN AND FIBRINOGEN IN FATAL ERYTHROBLASTOSIS FETALIS

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A HEMORRHAGIC state not infrequently complicates the more severe types of hemolytic disease of the newborn (erythroblastosis fetalis). While attention has been focused by the serologists on the dramatic controversies of the antigen-antibody reaction which is the basis of this disease, severe subsidiary manifestations such as hemorrhage have been largely neglected. It is usual to explain these hemorrhagic manifestations on the basis of increased fragility or permeability of capillaries or deficiency of circulating prothrombin activity. Proof has been generally lacking. In the case here presented death was due to intra-alveolar pulmonary hemorrhage. Prolonged fluidity of withdrawn venous blood was found to be associated with fibrinogen deficiency complicated in turn by a prothrombin deficiency.

CASE REPORT

A white female infant was born spontaneosuly but prematurely (birth weight 1,900 grams) to a 29-year-old Rh-negative (cde/cde) mother. There had been two previous pregnancies: the first, ten years previously culminating in a healthy child, and a second, ending in a miscarriage at three months. At delivery the maternal serum contained a high titer of Rh antibody (specificity: anti-D: reactivity and titer: saline 1:20,000, 20 per cent bovine albumin 1:5,000). There was no record as to how long in the present pregnancy these antibodies had been present.

At birth the child was pale, slightly jaundiced, with labored respirations. A few purpuric spots were noted beneath the skin of the abdomen. The Coombs test initially reported as negative was repeated on admission to this hospital, and found to be positive.

The infant received a transfusion 70 ml. of whole citrated Rh-negative blood via the internal saphenous vein before being transferred to St. Mary's Hospital for an exchange transfusion.

On admission to St. Mary's Hospital six hours after birth the child was moribund. Examination revealed mild icterus, but respirations were labored and gasping and there was severe pallor and a slight degree of cyanosis. The infant was limp and there was general loss of muscle tone. A small amount of frothy, blood-tinged mucus was aspirated from the pharynx.

The blood showed a severe anemia with erythroblastemia. Erythrocytes were 1.91 million/mm.^{3}; hemoglobin was 6.6 grams per 100 milliliters. The nucleated cell count was 58,000/mm.^{3} of which 99 per cent were erythroblasts. The infant was also moderately jaundiced, the van den Bergh test showing bilirubin levels of 11.1 mg. per 100 ml. in one minute and 18.0 mg. per 100 ml. in thirty minutes.

An exchange transfusion using O-Rh negative (cde) citrated whole blood was commenced. Owing to difficulty in entering the umbilical vein, the catheter was inserted in the right saphenous vein at its junction with the femoral vein. Units of 20 ml. were exchanged in sequence. During the procedure there was an increase in petechial spots on the abdomen. After six exchanges in thirty minutes, the infant ceased to breathe. Stimulants, withdrawal of blood, and artificial respiration were all ineffective.

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Fig. 1.

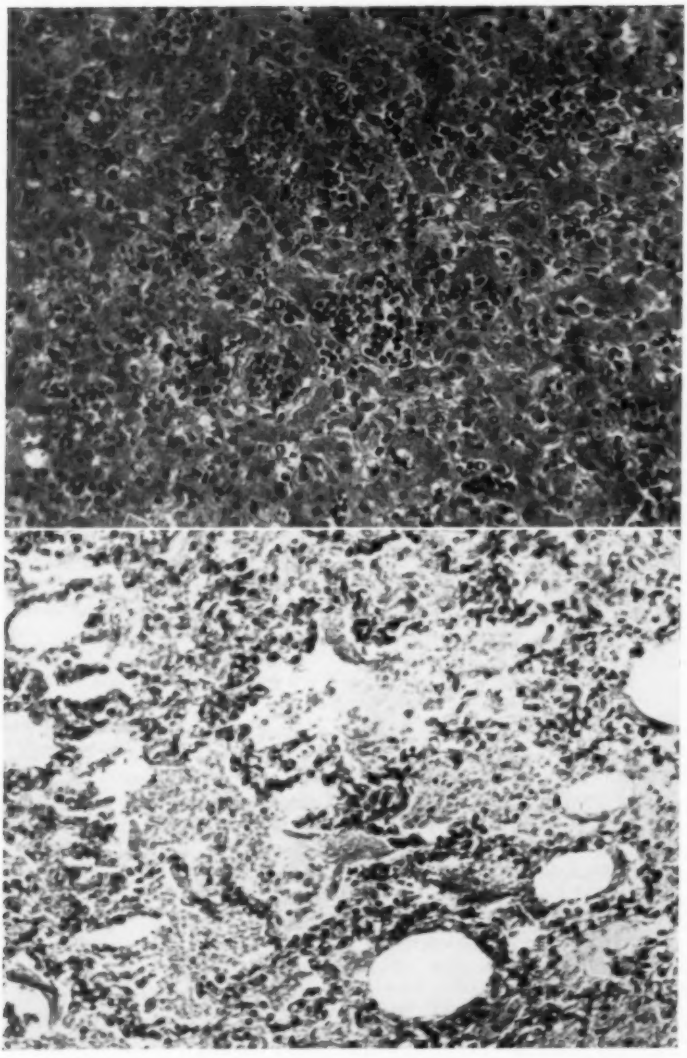

Fig. 2.

Fig. 1.—Section of infant's liver stained with hematoxylin and eosin, showing foci of immature erythroblasts, intact liver parenchymal cells, and prominent sinusoids. (×250 approximately.)

Fig. 2.—Section of infant's lung stained with hematoxylin and eosin, showing excessive intra-alveolar hemorrhage which was the immediate cause of death. (×250 approximately.)

The infant had lived seven hours from birth.

Autopsy.—An autopsy was performed six hours after death by Dr. John Howell. The results of the study are summarized as follows:

1. Jaundice. There was mild jaundice of the skin which did not extend to the scleras. There was no noticeable jaundice of the internal organs, including the brain.

2. Extramedullary hematopoiesis with hepatomegaly (210 grams) and splenomegaly (75 grams). Sections of these enlarged organs showed many islands of hematopoiesis. In these the erythroblasts were large and immature, suggesting an arrested maturation. The liver parenchyma showed no lesion, but the sinusoids were distended. (Fig. 1.)

3. Hemorrhagic diathesis. There were scattered petechiae and ecchymoses beneath the pleura, pericardium, peritoneum, and dura. In addition there was extensive intra-alveolar pulmonary hemorrhage (Fig. 2). This involved large portions of the lungs, particularly the lower lobes. The intervening lung tissues were well aerated.

Coagulation Defect.—Interest was focused on the hemorrhagic condition. Venous blood withdrawn at the time of the exchange transfusion did not clot at room temperature for seventy-two hours! Addition of an excess of thrombin to this blood rapidly produced a small filmy coagulum. It was therefore concluded that a serious quantitative fibrinogen deficiency existed.

An estimation of the fibrinogen level was made as follows: The fibrin coagulum produced from a measured volume of plasma by the addition of the thrombin was thoroughly rinsed in serial saline washes. The coagulum was then digested with a measured volume of trypsin of established nitrogen content. The pH was adjusted with phosphate buffers to 8.0 and the nitrogen content of the mixture was then estimated after acid digestion and nesslerization. The value of the trypsin nitrogen was then subtracted from the total nitrogen, leaving fibrin nitrogen. Multiplied by protein conversion factor (6.25), the result gives the fibrinogen weight.

Values of 0.4 to 0.5 gram per 100 ml. are found in normal plasma by this method. In the present case, a level of 0.12 gram per 100 ml. was recorded. A control plasma at the same time yielded a value of 0.50 gram per 100 ml. Since the estimation followed an infusion of normal blood amounting to from 25 to 35 per cent of the estimated total circulating blood volume, the initial levels of fibrinogen must have been considerably lower, if not completely absent.

There was also a prothrombin deficiency. This was estimated by the one-stage technique at 11 per cent of activity at the onset of the exchange transfusion and 16 per cent of activity at the fourth change. Although in the absence of normal amounts of fibrinogen, the validity of the one-stage procedure is open to question, in this instance some degree of prothrombin deficiency was probably present. The residual fibrinogen clotted readily on the addition of thrombin.

It is not possible to exclude the possibility of a combined deficiency of AC globulin (labile factor of Quick). A procedure such as Owren's one-stage method[2] would have been of definite value in assessing this feature.

DISCUSSION

Hemorrhagic complications, sometimes fatal, have been observed on several occasions in severe hemolytic disease of the newborn. In the present instance deficiencies of fibrinogen as well as prothrombin were found.

Death was due to intra-alveolar pulmonary hemorrhage. The occurrence of severe respiratory distress, blood-tinged bronchial secretions, and subepithelial petechiae before the exchange transfusion indicate that hemorrhages had developed before the transfusion was commenced. It is

possible that the infusion of a single transfusion of 70 ml. and also the repeated changes of 20 ml. during the exchange transfusion may have accelerated the hemorrhage by increase in pulmonary arterial tension. It is of utmost importance in this disease that transfused blood be injected slowly, so that the pulmonary circulation is not overloaded.

Of the seven cases of congenital afibrinogenemia collected by Henderson, Donaldson, and Scarborough,[1] the blood from one case remained fluid after standing for thirteen days in the test tube. This fluidity of blood for prolonged periods is a feature of fibrinogen deficiency. One precaution is necessary in assessment of this feature: the standing blood should be under direct observation for several hours at the onset. This will eliminate the possibility of an early clot forming which subsequently redissolves by excesses of fibrinolytic activity.

Fibrinogen deficiency produces prolonged clotting times. In this case the blood was fluid after three days! Fibrinogen is synthesized in the liver. Liver damage is an important facet of the pathology of hemolytic disease of the newborn. Although on occasion frank liver necrosis can be shown in these cases, in the present case histological studies did not reveal signs of morphological damage in the parenchymal cells of the liver (Fig. 1). This finding does not, however, exclude the possibility of functional damage to these cells.

It is of interest that Wiener and associates[3] have recently observed fibrinogen deficiency in immunized Rh-negative mothers in whom the fetus was already dead in utero. In each of their three cases there was resultant severe maternal hemorrhage. In this case the mother gave no history of excessive bleeding during labor or post partum.

Primary congenital afibrinogenemia is a rare disease. Seven published cases only were collected by Henderson and co-workers in 1945.[1] Afibrinogenemia in these cases occurred in consanguineous matings, indicating that in such instances the fibrinogen defect is probably inherited as the effect of homozygous recessive genes. There was no history of consanguinity in the present case. Chance association of primary congenital afibrinogenemia and hemolytic disease of the newborn is mathematically highly improbable. The fibrinogen defect in this present case is, therefore, most probably related to the hemolytic disease.

Prothrombin is also synthesized in the liver and the deficiency detected in the present case may have been the result of the ineffective synthesis by the fetal liver. Prothrombin deficiencies are a not infrequent finding in hemolytic disease of the newborn.[4] Although the mother did not receive vitamin K, her diet is stated to have been adequate.

SUMMARY

Fatal pulmonary hemorrhage in a case of hemolytic disease of the newborn (erythroblastosis fetalis) was associated with a fibrinogen deficiency and an associated prothrombin deficiency. The deficiency was not correlated with morphological damage to the hepatic parenchyma. These defects were associated with a high maternal titer of saline and albumin antibodies.

Our sincere appreciation is tendered to Dr. J. Eto, Instructor in Pediatrics, for his assistance in assembling the details of this case.

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MEDIASTINAL LYMPHOSARCOMA IN AN INFANT

Twelve-Year Survival Following Radiation Therapy

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THE purpose of this paper is to record in the literature a case of primary mediastinal lymphosarcoma in a 7-month-old infant who was apparently cured twelve years after x-ray therapy. Thorough search of the literature has failed to reveal a reported five-year survival for any infant case of lymphosarcoma or for any case with mediastinal involvement at any age.[1-9, 13-15]

CASE REPORT

The patient (R. T.), a Puerto Rican female, is now 13½ years old. Her illness dates back to the age of 7 months when, on July 25, 1939, she was brought to the pediatric clinic because of cough and fever of several weeks' duration. A chest plate revealed a large intrathoracic mass in the mediastinum and the parents were advised to have the child admitted to the hospital for biopsy and therapy. However, they did not return until seven months later when the child was admitted on Feb. 29, 1940. Her symptoms at this time were similar to those when first seen.

The baby had been a normal full-term delivery and there had been no previous illnesses. The family history was noncontributory.

Examination on admission revealed a well-developed, well-nourished infant in no distress. Positive physical findings were limited to hypertrophied tonsils and one small node palpable in the left axilla. There was no other significant adenopathy and the spleen and liver were not felt. Blood studies revealed a hemoglobin of 65 per cent, red blood cells 4.95 million, and white blood cells 12,900 with 80 per cent polymorphonuclear leukocytes and 20 per cent lymphocytes.

From the Brooklyn Cancer Institute.

A chest plate (Fig. 1) showed the mediastinal mass still present. A Silverman needle biopsy of the lesion (Figs. 2 and 3) was reported as follows: "The section consists of atypical cells. They are discrete, round or polygonal in outline, with a scant, pink cytoplasm, and round, ovoid or irregular, usually hyperchromatic, nuclei. The nuclei vary moderately in size. There is invasion of bits of fibrous tissue. The cells show no tendency to arrangement in rows or glands. Diagnosis: large cell lymphosarcoma."

Fig. 1.—Chest x-ray showing mediastinal mass.

Between March 18 and April 17, 1940, a total dose of 1360 r. units of x-ray was applied to the mediastinum, half anteriorly and half posteriorly. On the patient's next visit to the hospital in June, 1940, the mediastinal lesion was almost gone and a plate taken in November, 1940 (Fig. 4), showed no evidence of the mass.

During the next twelve years the patient was brought to the hematology

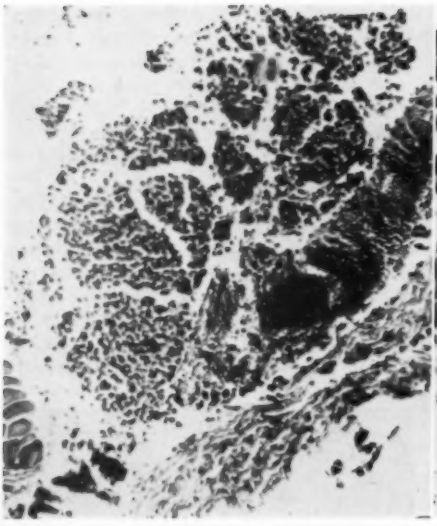

Fig. 2.—Biopsy of mediastinal lesion. (×118.)

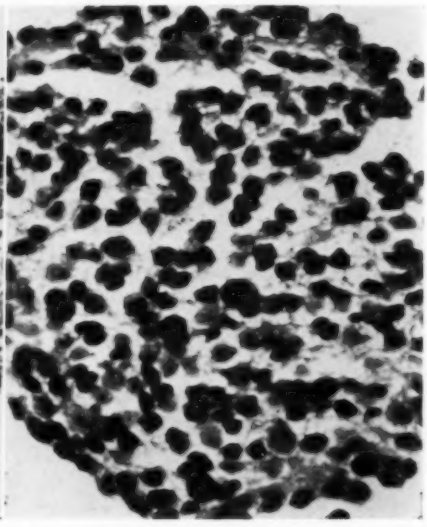

Fig. 3.—Biopsy of mediastinal lesion. (×500.)

Fig. 4.—Chest plate five months after x-ray therapy. The mediastinal mass has disappeared.

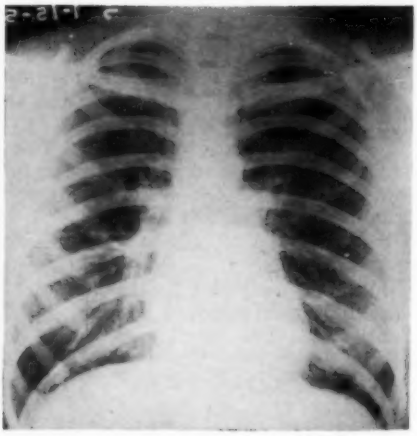

Fig. 5.—Normal chest plate twelve years after x-ray therapy.

clinic at six- to twelve-month intervals for examinations, blood counts and chest x-rays. All have been completely normal. In 1942 a tonsillectomy and adenoidectomy were performed and pathological studies revealed no evidence of lymphosarcoma. The most recent clinic visit was on Jan. 15, 1952, at which time the hemoglobin was 91 per cent, red blood cells 4.99 million, and white blood count 7,900 with 62 per cent polymorphonuclear leukocytes, 4 per cent monocytes, and 34 per cent lymphocytes. A chest plate (Fig. 5) taken that day was entirely normal.

DISCUSSION

Lymphosarcoma is a malignant neoplasm stemming from reticuloendothelial and lymphocytic cells. There are three cytological subdivisions, namely, the large cell or reticulum cell variety, the small cell or lymphocytic type, and the giant follicular lymphosarcoma. There are differences of opinion as to whether the reticulum or lymphocytic type has the worst prognosis, but all studies reveal the giant follicular variety as being the least malignant. All varieties are markedly radiosensitive and there are frequent dramatic clinical remissions following this type of therapy. However, the prognosis for life expectancy is poor with the average duration from time of diagnosis to death being less than twenty-four months.

There have been a number of excellent studies of ultimate prognosis following all types of therapy. Stout,[12] in a review of 170 cases (119 of which were definitely known to have received treatment), found that only fifteen were without evidence of the disease at the end of five years, the same fifteen still being apparently cured at the end of ten years. Thirteen others died of the disease after five or more years while one was dying ten years afterward. Seven of the apparently cured patients had been treated with radiation alone, three with surgery alone, and five with surgery plus radiation. Eight of the original cases had the primary site in the mediastinum and none of these lived five years. No patient under 30 years of age had a five-year survival. Stout stated that in his experience lymphosarcoma in childhood was almost invariably fatal.

Sugarbaker and Craver,[5] in a series of 196 patients (all but two of whom were treated), reported fourteen alive and well after a five-year interval since therapy, while seven others were dying of the disease after five years. One hundred sixty-four of their patients had been treated with radiation alone, eight of these being among the apparently cured cases. Thirty had been treated either with surgery alone or surgery plus radiation and of these six were apparently cured. Their patients ranged in age from 4 to 88 years with a rather uniform distribution by decades. The average life expectancy under the age of 30 was 11.3 months and only half that for those over 30. Only one of their patients under the age of 30 was still alive five years later.

Diamond[10] states that treatment for lymphosarcoma in childhood is unsatisfactory and poor, a fatal termination within a period of a few weeks to a few months being invariable.

Andrus and Heuer[11] find that lymphosarcoma is the commonest type of mediastinal tumor in all large series in which careful pathological studies are made. They state that therapy is palliative at best, although temporary remissions may be brought about by intensive radiotherapy. However, they continue, the disease is uniformly fatal and pursues a rapid course, the average duration of life after the onset of symptoms being under one year.

SUMMARY

1. A case of primary lymphosarcoma of the mediastinum occurring in a 7-month-old infant is reported. Rapid disappearance of the neoplasm

followed 1,360 r. units of x-ray therapy and the child has been asymptomatic and apparently cured for the past twelve years.

2. The diagnosis of lymphosarcoma is not a hopeless one. Apparent cures do occur following prompt and adequate therapy.

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Medical Progress

PINK DISEASE (INFANTILE ACRODYNIA)

A Physiological Approach. (An Evaluation of Adrenal Function and the Importance of Water and Electrolyte Metabolism)

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Introduction, Historical, and Symptomatology

There are few diseases in pediatrics which present such a complexity of symptoms, and few other conditions reveal such a picture of prolonged stress and misery. Doubtless there are few other circumstances where the pediatrician feels more embarrassed at his own therapeutic inactivity and more uncertain of his ability to retain the confidence and cooperation of the parents.

Clinicians from all countries of the world have been impressed by some particular aspect of the bizarre pattern of this symptomatology. They have respectively placed emphasis on different aspects. They have endeavored to support a virus etiology, either neurotrophic or respiratory, to prove a vitamin deficiency, to incriminate a toxin or poison, or to fall back on allergies, to single out some particular region of the central nervous system or of the autonomic nervous system, or indeed, as recently, to suggest psychosomatic origins.[1] But surely, if nothing else, this modern age has taught us to examine disease processes in terms of altered physiological conditions, and to fortify our knowledge of symtomatology and our clinical approach by means of biochemical assay. It is not the purpose of this manuscript to consider in any detail the possible etiological causes, the literature concerning which is voluminous, and has been reviewed elsewhere,[2] but to direct attention to alterations in physiology and to the departure from homeostasis, which has previously been my particular interest.[2-8] It will be obvious that such knowledge in respect to this disease is not complete nor entirely free from speculation, but it is hoped that enquiry will be stimulated on the part of others to pursue further this work and this approach, which has hitherto been neglected.

It was unfortunate that the first clinical description of this disease given by Selter of Germany in 1903 aroused such little interest.[9] He presented eight female children about 2 years of age suffering from a condition he termed "trophodermatoneurosis." Following Selter, silence reigned until the year 1914 when the Australian physician, Swift,[10] gave an accurate description of the condition in its infantile manifestation. Prior to Swift's paper, the condition had not entirely escaped attention in Australia, as Charles Clubb of Sydney had already coined the name "pink disease," while William Snowball of

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Melbourne talked of the syndrome "raw beef hands and feet" as far back as 1883. As a result of this stimulus, Wood,[11] in conjunction with Hobhill-Cole, presented a study of ninety-one cases at the first Australasian Medical Congress following the First World War in 1920.

This disease was independently described by Bilderback of the United States in 1920 at Seattle, Wash. His excellent description clearly defined the manifestation in children as well as in infants. In the same year, Weston of Columbia contributed the name "acrodynia,"[12] and soon reports and observations became numerous. In the following year an important paper was published by Brown, Courtney, and MacLachlan of Toronto, Canada,[13] while, in England, Weber[14] drew attention to this disease, and it was described in France by Comby,[15] and for the second time in Germany by Feer[16] in 1922.

It is known that the sexes are equally affected. The question of seasonal incidence has through the years been a matter of some argument. But it has been shown in America,[17] in Australia,[18] and in England[19] that the seasons play no part. However, geographical location definitely does influence the incidence of this disease. Pink disease is not uncommon in Australia—any large hospital there will have at least one or two cases, either as outdoor or indoor patients, attending. In the state of South Australia, with a population approximating a half million inhabitants, there are at least 80 to 100 patients each year suffering from this condition; whereas in the state of Connecticut in the United States, with a much larger population, it is rare for one case to present in a year. It has been my impression from my own study of this disease (and from interrogation) that it is much more common in Australia than in America, England, Canada, or Europe. Perhaps more interesting still is the regional distribution of this disease within countries themselves, which has been so clearly shown.

From information gained through hospital records[3] and through a personal study of cases, it has been found repeatedly that 80 to 90 per cent of cases in Australia occur between 6 months and 2 years of age. From other data it is apparent that the same holds for Canada[20] and England.[19] It is of some interest that the curve of the age incidence follows so closely that of infantile allergic phenomena.[3, 21] Eosinophilia, if looked for in pink disease with appropriate methods, will sometimes be found.[6] In any large series of cases one finds occasionally the occurrence of more than one case in the same family of siblings; and it has also been the experience of the author, and of other workers, to find recurrences of this disease.[2]

SOME OBSERVATIONS RELATING TO SYMPTOMATOLOGY

The complexity of symptoms and signs and the bizarre nature of these impress all pediatricians and physicians who have met, and do meet, cases of this fascinating disease. It is not intended that a detailed description be given of these well-known phenomena, but rather to briefly point out some relevant aspects which have been obtained by experience with over 100 cases.

The Infantile Form.—The pediatrician or physician is consulted be-

cause of a sudden change of well-being on the part of the infant. There may be a history of a cold, or of recent infection associated with rhinitis. Irritability is present and the little patient, usually aged 5 or 6 months or older, refuses to take his food. Teething is in progress, and the mother often ascribes the state of her infant to this. Indeed it is often not until weight loss becomes remarkable, which is early, that the family doctor becomes suspicious of a more pernicious condition. The pediatrician is sometimes confronted with the child who has been referred to him from the ophthalmologist, the mother having consulted an eye specialist in the belief that photophobia is the main cause of the condition.

Examination at this juncture reveals that sweating has become noticeable, and that the hands and feet of the infant show a slight pinkness, and perhaps an unusual cold and moist feeling. The infant markedly resents examination and tends to burrow his head into the pillow away from the light. The skin temperature is usually normal, but may be depressed or elevated one degree. The mother complains that the child cries most of the night, that he has become constipated, or (and this is less common) that one or two relaxed bowel actions have been passed. If the opportunity presents itself, tachycardia and hypertension can be clearly defined in all cases.

Following this insidious onset the classical picture develops. Anorexia becomes marked, sweating profuse, and the hypertrophy of the sweat glands which is seen microscopically is emphasized by miliarial or sudaminal rashes which spread across the trunk of the body. As the disease progresses hypertension becomes easily detectable. The muscles are soft to the feel, and the hands and feet previously pink some of the time become pink, swollen, edematous, cold, and moist most of the time. That they are causing the infant distress is made obvious by the fact that one may observe the little patient rubbing them together. Any previous confusion of these symptoms with "measles" is now dispelled. The mother is generally very distressed; she is tired and exhausted from sleepless nights and from frequent fruitless efforts to force feed her infant. The resentment of the infant toward the mother is to her a matter for further concern. The prescribed sedatives of common usage in their usual dosages fail to produce their expected effect. The household is in a state of some disruption, and although textbooks warn against the dangers of secondary infection, the pediatrician more often than not admits the child to a hospital or to a nursing home to relieve the harassed parents for at least some of the time. Respiratory infection is the chief danger.[3] The weight chart reaches a steady low level with the passing of the weeks. With the shedding of the skin from the hands, which starts between the fingers, the tender "raw beef hands and feet" become manifest. The layers of skin become more delicate with each successive shedding. During periods of atmospheric heat, which are badly tolerated by these children, crying gives way to listlessness, apathy, and exhaustion. The hot, dry climate of Australia is singularly deleterious. There is always the potential danger of shock, collapse, and death. During periods of atmospheric cold the hands fre-

quently become cyanosed. This picture of extreme misery and stress usually continues for several months, even up to 18 months, or longer. However, a minority of cases may be mild, with only two or three months' illness. Diarrhea presents in a smaller number of cases, and in my opinion is not usually of infective origin. The prognostic significance of this is grave.

As insidiously as they came, so the symptoms gradually disappear; the irritability subsides, sleep improves, feeding is no longer forced, and the first smile appears on the little face. Recovery begins. This is complete in the vast majority of cases. However, in my experience a state of "athrepsia" or "failure to thrive" may continue in some infants for several months—long after the extremities and cutaneous signs have disappeared.[6] In other cases the condition persists in a milder form throughout several years of childhood. Bronchiectasis in preadolescence is sometimes a sequel of pink disease. Indeed, in Australia pink disease is a common cause of bronchiectasis.

The Older Child.—The manifestation in older children is not so frequently encountered, and the diagnosis is often more difficult to make unless the classical picture of the extremities is exhibited. This is rare and I[3] have encountered it in only one child 5½ years of age. The thicker layer of skin of older children does not so readily reveal pinkness of the hands, but coldness and moistness are in evidence, and peeling of the skin generally occurs.

In contrast to the infant, the symptoms of lassitude, fatigue, and inertia predominate. A fractious or even violent nature of a child previously of a normal happy disposition is characteristic. The sick child stops walking and may only want to "sit all day," becomes asocial, and talks infrequently. Long periods of nocturnal wakefulness are experienced. Sweating, though abnormally increased, is not so much in evidence objectively. Food and fluid demand is minimal, and constipation is nearly always present. Marked photophobia does not so often present in such an obvious way, but is rather shown by a resentment to bright light, or by the child's insistence to undress in the dark. The diagnosis is not generally made until this picture has been present for some months, and until a failure to gain weight is of several months' duration. Hypertension and hypotonia are detectable.

The course of the illness is extended over many months, usually more than a year, and it is of interest that allergic phenomena seem to be closely associated. Six out of eleven patients of this category previously reported[6] showed either "wheezes in the chest" or recurrent bronchitis or actual asthma, skin rashes, and a significant eosinophilia was demonstrated in ten out of eleven cases. On the other hand, Holzel and James,[22] by investigating a large series of cases, found no evidence that allergic disorders in pink disease are more common than in the normal child population.

CONCERNING THE ETIOLOGY

The Role of Mercury.—One of the brighest and most hopeful etiological facts in the history of the disease has been the discovery of an increased

amount of mercury in the urine of these children with pink disease, findings which have been provided by the work of Warkany and Hubbard of Cincinnati[23, 24] and other workers.[22, 25-27] In their most recent paper, Warkany and Hubbard show significant amounts of mercury in the urine of thirty-eight out of forty-one cases. These workers have gone far to establish an "idiosyncrasy" to mercury, as an important factor in our present understanding of the causation of pink disease. However, as to why such an idiosyncrasy should occur, or what factors are related to it, are unknown. The fact that some children are given mercury after the true onset of the disease in the belief that "teething troubles" are being treated causes some confusion and a difficulty in interpreting the significance of the urinary mercury estimation. Normal children of the same age group who have ingested nontoxic forms of mercury can excrete equal amounts without manifesting this disease. This emphasizes that the crux of the matter rests with elucidation of the "idiosyncrasy." This is also emphasized by the failure of Dimercaprol (BAL) to produce consistently effective results.[22, 23]

Investigations performed at Great Ormand Street, London, have led to the conclusion[26]: "In view of the conflicting evidence, the theory that ingestion of mercury is the cause of pink disease should be given the Scottish verdict of 'not proven.'"

Warkany[23] has found this metal to be present in 92.7 per cent of his cases investigated, Fanconi and Botsztejn[25] in nineteen out of twenty cases, and Holzel and James[22] in sixty-one out of ninety-four. Warkany noted that occasionally in the same patient the excretion of mercury varied greatly from one sample of urine to another, and sometimes the urine specimen was free of mercury, or contained very small amounts. It has not been possible to find a correlation between the amounts excreted and the severity of the disease. However, there is little doubt that patients with pink disease excrete more mercury than normal control children.

Normal children can absorb and excrete small amounts of mercury without showing any signs of untoward symptoms; hence, Warkany suggests that an individual susceptibility ("idiosyncrasy") to mercury intoxication exists in the children who develop pink disease: "Just as some persons react with asthma or hay fever to environmental conditions well tolerated by others."

In other words, it is suggested that we are dealing with a syndrome akin to drug sensitivity or to an allergic phenomenon. Since the recurrence of this disease is the exception and not the rule, it must be further postulated that we are not dealing with a permanent idiosyncrasy.

The observation that the interval between the administration of mercury and the onset of the disease varies from one week to several months also requires elucidation. This was noted in the cases of Warkany and those reported by Fanconi and Botsztejn.[25]

I suggest that as mercury essentially leads to denaturation of cellular protein and destruction of cells, adequate attention should be given to the possibility of sensitization to cellular protein liberated by mercury in-

gestion; that is, a state of autosensitization should be considered just as recent research work on nephritis leads us to believe that the nephrotic syndrome is maintained by autosensitization to proteins arising from disintegration of the basement membrane of the glomerulus (Proceedings of the Society for the Study of Nephrosis, New York, December, 1951).

Warkany, possibly through a lack of clinical material, has been unable to demonstrate any association of allergic phenomena with pink disease. He gives an impressive comparison of the symptomatology with that of mercury poisoning. He fails to point out, however, that many phenomena which are characteristic of mercury poisoning, such as loss of teeth, gangrene of the mucous membranes, necrosis of jaw bones, and tremor, are rare in pink disease. On the other hand, several features of pink disease, such, for example, as hypertension, are not recognized symptoms of mercurial poisoning.

It is sometimes dangerous to compare diseases of known etiology, such as mercury poisoning, with diseases of unknown origin. Although pink disease shows nearly all the features of mercury poisoning in its different phases, the same could be said of other agents. In particular, one might mention, for example, a disturbance of porphyrin metabolism. Indeed hypertension, tachycardia, sweating, abdominal pain, muscle weakness, photosensitivity, psychological change, edema, cachexia, oliguria, peripheral neuritis with paresthesia, albuminuria, and constipation are all included as concomitant features.[28] Metallic poisoning itself is one of several factors that can give rise to disturbances in porphyrin metabolism.[29]

It is perhaps of interest that cursory attention to this fact showed a slightly raised coproporphyrin excretion in four children studied with pink disease as compared with twelve normal children.[6] From observing numerous samples of plasma taken from these cases, it became apparent that a peculiar orange-brown tint was often revealed, which allowed one to distinguish it with the naked eye from samples taken from normal children. Spectrographic absorption tests revealed this to be due to an excess of oxyhemoglobin in the plasma. Whether an intravascular hemolysis due to hemoconcentration or toxic factors occurs, was not determined.

Fanconi and Botsztejn[25] regard pink disease as a "neuro-allergic condition." Landolt and Egli,[30] also of Switzerland, found allergic disorders in 32 per cent of former patients who had had pink disease. However, Holzel and James[22] found no evidence, in their cases, of an allergic response to mercury.

These latter workers demonstrated a mild response to Dimercaprol in twelve out of fifteen infants, but a good response in only three. They showed that in the district around Manchester, where pink disease is common, the administration of "teething powders" is less frequent than in the county of Warwick, where the disease is rare. Over 1,500 interrogations were made in each district. In the three cases quoted that did respond to Dimercaprol, the characteristic clinical picture of pink disease was not manifest. These cases also exhibited a rise in serum-cho-

lesterol. This was regarded as evidence that chronic ingestion of mercury produces changes in the serum-cholesterol, probably due to renal damage, simultaneously with symptoms like those of pink disease. The finding of significantly low blood cholesterol levels has been my experience.[6]

If mercury is important in the etiology of pink disease, and indeed the evidence is strong, we can in no way assume that this disease is due to clearly defined poisoning. The role of mercury is probably only one factor which disturbs the equilibrium of either enzymal or hormonal systems, and possibly penetrates the natural defense mechanisms against allergic reactions.

The Nervous Child and Pink Disease.—The manifestation of pink disease in older children was adequately defined by the French physician, Rocaz,[31] as the "forme nerveuse," and by the German writers as a "form fruste."[32] It has received comparatively little attention by the English-speaking world.

It is of interest that such children as these are disturbed emotionally; they are "nervous children" and indeed, as pointed out previously,[6] they conform to the "nervous child syndrome," a somewhat nebulous condition described by Cameron in 1919.[33] Whether or not stress and psychosomatic changes can produce such organic changes is yet to be determined.

It is of interest that Leys and Cameron[1] recently investigated the family setting and environment of six unselected cases of pink disease. They concluded that: "The evidence of stress in the family situation of these cases is striking and indeed more obvious than that in the families of many children attending the psychiatric clinic." There was a distinct lack of maternal warmth in all cases, and five out of six were obviously unwanted children. The stress of emotional deprivation is thus emphasized as being important in the etiology of this disease.

Bernheim and Confavrecia[34] have reported on the beneficial effects of electric shock therapy with induced convulsions as a means of control of the mental and emotional disturbances in these older children with pink disease.

The Autonomic Nervous System.—Feer[35] was the first to emphasize that a possible overaction of the sympathetic nervous system existed in pink disease, and many others have supported this view that the hypertension, tachycardia, sweating, and occasional hyperglycemia provided evidence of such a disturbance. Stolz and Woringer,[36] and also Albertini[37] claimed to have found hyperplasia of the chromaffin system. Blackfan and McKhann[38] noted that the pulse rates of patients with acrodynia differed from those of normal subjects in that they did not vary with crying or during sleep. Day and associates[39] measured the electrical impulse of the heartbeat with a special recording device. They noticed the effect on the heart rate produced by changes in emotion and following the injection of the drugs atropine, Adrenalin, ergotamine tartrate, and Mecholyl. These authors reached the conclusion that emotional disturbances failed to evoke certain normal responses from the vegetative nervous system in pink

disease. They thought that this failure of the sympathetico-adrenal response to emotion could well arise from the fact that the sympathetic nervous system in a patient with acrodynia might already be overstimulated to such an extent that it could no longer react to further stimulation. It was suggested that a possible similarity existed between children with infantile acrodynia and subjects with pheochromocytoma, although an alternative view was also taken that the hypertension and tachycardia possibly resulted from widespread vasoconstriction due to some obscure toxin.

Glanzmann[32] also sugested that the adrenal medulla produced an increased secretion of adrenaline in pink disease. He investigated this by noting the changes in the iris of an enucleated frog's eye which had been placed in Ringer's solution, to which had been added plasma samples from patients with pink disease. These plasma samples were found to have a strong mydriatic effect, detectable even in a dilution of one in a million. No effect was found with plasma samples from normal children. Glanzmann suggested that a raised blood adrenaline level was responsible for these effects.

The sympathetic branch of the autonomic nervous system has received the most comment. It has never been shown, however, how hypertension, tachycardia, and hyperglycemia which are features of sympathetic nervous stimulation can be reconciled with salivation, rhinorrhea, muscle weakness, and sweating, which are all indicative of stimulation of the parasympathetic system.

It is of interest that newer knowledge concerning the behavior of certain poisons (the organic phosphates) offers one possible mode of explanation of the above phenomenon. The destruction of serum cholinesterase can lead to both strong parasympathetic stimulation as a result of the collection of acetylcholine (muscle paralysis, areflexia and hypersecretion); and at the same time the adrenal medulla is stimulated with the liberation of adrenaline. The cholinergic, preganglionic fibers of the splanchnic nerves are stimulated by acetylcholine. These fibers supply the adrenal medulla. Hence hypertension, tachycardia, and hyperglycemia can be concomitant features. Such a combination of effects is seen in poisoning with parathion (p-nitrophenyl diethyl thiophosphate) or "nerve gas," which is extremely lethal in small amounts.[40] Thus attention is again directed to a toxic agent.

It has been shown that there is no gross or remarkable rise in the blood adrenaline in pink disease.[6] Eighteen cases were investigated along with twenty-four normal children.

The Adrenal Gland.—Investigation of hemoconcentration and plasma sodium and chloride levels (to be discussed presently) revealed a diminution of these electrolytes.[2, 4] On the basis of this loss of plasma sodium and chloride, I first thought that the condition of pink disease might be associated with a relative adrenal insufficiency of the so-called "salt and water corticosteroids." It was thought that such an insufficiency could possibly be occasioned by specific and nonspecific "stress-producing agents" (from emotional changes to mercury poisoning). The malady was thought

to be prolonged by the actual stress of the disease itself, which is so apparent clinically.

Such a concept was to borrow directly from the work of Selye,[41] and indeed as pointed out in a previous paper, almost all the biochemical changes and observable features of the "alarm reaction" are manifest by the condition of pink disease.[5]

The age incidence of this disease falls predominantly in that period of development when the adrenal gland undergoes remarkable changes, the reasons for which are as yet still obscure, and have again recently been convincingly demonstrated by the work of Tahka.[42] Conditions which are referable to a disturbance of the "salt and water hormone" have of late received much attention in the pediatric literature and are reviewed elsewhere.[5] My concept was strengthened by the fact that the first sixteen patients treated by the oral administration of 6 to 8 Gm. of salt, with or without 2 to 4 mg. of desoxycorticosterone acetate, gave very encouraging results clinically. Some of these patients in a matter of days showed striking and even dramatic improvement. Anorexia disappeared, sleep became undisturbed, and irritability gave place to a happy disposition. Older children lost their lassitude and became noticeably energetic. It seemed that an illness of many months had been reduced to a matter of weeks. Such striking improvement with this therapy has since been reported by some other clinicians.[43, 44]

As pointed out by Homer-Smith,[45] most of the physiological disturbances seen in adrenal insufficiency appear to be secondary to oligemia, since they can be partly or wholely alleviated by the administration of sodium chloride. It is natural that oligemia or chloride and sodium depletion, from any cause, produces a picture resembling adrenal insufficiency.[46]

Later therapeutic investigations undertaken, using salt and steroid in a series of seventy cases, revealed that some showed little or no improvement: the photophobia, pinkness of the hands, loss of weight and muscle weakness of the infant sometimes seem to "be little, if at all mitigated." This evidence supported by hormonal investigation led to the conclusion that changes in electrolyte and water equilibrium found their origin outside of the adrenal gland, and it was suggested that attention be given to the kidney tubule.[6, 7]

In view of the close resemblance between most aspects of the symptomatology of this disease and "adrenal stress" it was necessary to undertake hormonal determinations to further elucidate this aspect.

Investigation of twelve cases using the technique of Venning and associates[47] revealed normal glucocorticoid excretion in the urine. The 17-ketosteroid determination was found to be slightly but significantly raised, and the reaction of the circulating eosinophil cells to Adrenalin was found to be normal in response.[7] The estimation of the blood adrenaline content using the technique of Shaw[49] as modified by Raab[48] has already been referred to.

The possible relationship between pink disease and Selye's alarm reaction has been considered elsewhere.[5] My investigations led Selye to discuss pink disease in his treatise on stress,[50] and to include it as a disease of adaptation. Bearing all the

available evidence in mind, it is difficult to believe that an alteration of the vegetative adrenal system is of more than secondary importance in this disease. That this mechanism is involved to some extent seems almost mandatory. The rise in 17-ketosteroid excretion is significant. The failure to demonstrate an elevation in urinary glucocorticoid levels is not disturbing. The work of Nichols and Miller[51] has shown that in some conditions of sweating the loss of glucocorticoid through the sweat may be significantly high, even though urinary excretion is normal. The conclusions of Bornstein and Trewhella[52] seem therefore somewhat premature. Indeed, as pointed out by Sayers,[53] until we know more concerning tissue utilization of adrenal hormone from blood assay, the value of glucocorticoid excretion will remain of limited value. The presence of an electrolyte disturbance itself throws a definite load on the adrenal gland, and herein probably lies one mode of involvement of adrenocortical function—nor can we disregard the obvious stress of the condition itself which is so apparent clinically.

PHYSIOLOGICAL CONSIDERATIONS

Carbohydrate Metabolism.—It has not been my experience to find high glucose tolerance curves as described by other workers.[32, 38, 54] Nor have the blood sugar levels, fasting or nonfasting, been above normal limits. Published and unpublished glucose absorption curves have shown, in some cases, a flattened contour.[4] Such alterations in the behavior of glucose absorption could find explanation in the work of Clark and MacKay.[55] These workers demonstrated alterations in carbohydrate metabolism in the presence of electrolyte disturbances and reductions of blood volume.

The Peripheral Vascular System.—The extremities are painful with subjective paresthesia, and show coldness, edema, erythema, and sweating with cyanosis during cold atmospheric temperatures. The circulation through the extremities is retarded. Shedding of the skin occurs and sometimes, but infrequently, ulceration leads on to gangrene. Skin color is dependent on capillary filling, and examination of the nail bed by direct microscopy has revealed a capillary bed which is open and apparently engorged with red blood corpuscles.

That the permeability of the capillary walls is altered is evidenced by the edema present in the hands and feet. Indeed, this phenomenon was clearly shown in the face and scalp of one infant observed.[4]

The systolic and diastolic pressure is raised. There is tachycardia and a slow circulation through the extremities, so that it is reasonable to presume that there is a widespread arteriolar spasm in this condition.

The extremities manifest the "susceptible state of Lewis," as pointed out previously.[2] This state is known to be related to the effects of histamine and anoxia. It is of interest that resistance to histamine is lowered by an upset of the electrolyte balance, analogous to those induced by excision of the adrenal glands.[56, 57] Such resistance is restored by the administration of desoxycorticosterone acetate.[58]

The Importance of Water and Electrolyte Metabolism in Pink Disease.—Braithwaite[59] of Leicester, in an en-

deavor to evaluate the relationship of this disease to light and vitamin D, was led to determine blood calcium, phosphorus, and hemoglobin levels. He found that some of his cases revealed slightly elevated calcium levels, and that the hemoglobin was consistently raised. The latter observation he interpreted in terms of water loss due to sweating.

Because preliminary investigations[2] into the blood picture of ten patients with pink disease (aged 6 months to 2 years) revealed a mean erythrocyte count of 5,400,000 cells, and a mean white cell count of 13,500 cells, careful hematocrit, hemoglobin, and plasma protein estimations were undertaken in a further series of twenty-three cases.[4, 6] That hemoconcentration is consistent, significant, and an appreciable finding is evidenced by the values obtained.

Twenty-three Cases	
Mean hematocrit	45%
Mean hemoglobin	14.6 Gm. %
Mean plasma protein	7.3 Gm. %

These values exceed those for normal children of the same age. Some individual cases may show hematocrit readings as high as 55 per cent, a hemoglobin of 17 grams per cent, and a plasma protein above 8 grams per cent (venous blood).

It is little wonder, then, that earlier clinicians such as Van Bogaert,[60] Bruehner,[61] and Rocaz[31] mentioned polycythemia of 6 to 9 million cells; but perhaps it is a little surprising that a persistently raised white cell count was interpreted in terms of leukocytosis, and causative infection. The absence of a febrile state, of neurological sequelae, the noncontagious nature, and the sharply demarcated age grouping might have aroused suspicion. Attention to the differential white count reveals no significant shift in Arneth count,[2] and modern methods have been significantly unsuccessful in the detection of infective agents.[62] The evidence, in the absence of starvation, for consistent, definite, and convincing neuropathological changes at autopsy, is lacking.[63, 64] Cerebral congestion and edema are present.[65] Examination of pathological material has also led me to the same conclusions. Thorough microscopical investigation of the spinal cord and nerves revealed no significant changes in two cases.[2]

Anemia and hypoproteinemia are expected along with the associated anorexia. A rise of the reticulocyte count may alone reveal this latent anemia. The estimated hemoconcentration takes no account of anemia, so, if anything, such simple methods underestimate, to some extent, the loss of water from the blood volume. More detailed methods, as yet not undertaken,[66] may show an appreciable deficit of extracellular space; and it may not be so surprising that shock collapse and death sometimes supervene.[4]

Although these particular infants and children are dehydrated, we do not find thirst as a prominent symptom; nor is thirst by any means commensurate with the amount of fluid lost through the kidney in the earlier stages, or through the skin in the established condition. This observation is also emphasized by Craig.[67] Anorexia, muscle pains, loss of weight, weakness and oliguria are prominent symptoms of the usual clinical picture. In older children, the region around the eyes is often sunken with darkened shadows. Collapse and shock are a

potentiality. These are all features of hypotonic dehydration.

In the early stages of this condition, diuresis is characteristic,[68] while in the established case, oliguria is the usual finding. Rocaz[31] made the remark, "The urine is usually scanty, dark in color, of high specific gravity and charged with urea and salts." It has been my experience,[3] and that of others,[38, 69] to find albumin in the urine on several occasions. Indeed, in one case observed, hematuria, albuminuria, and casts were found in the absence of infection, and apparent from the outset of the disease.

In the series of older children reported suffering from pink disease over a period of several months, 48-hour urine collections were carried out. Taking six patients of about the same age (2¼ to 3 years), or Cases 2 to 6, inclusive, and Case 8 of this series, it is seen that the mean urinary twenty-four-hour volume is 270 c.c. or 21 c.c. per kilogram per day (mean weight equals 13 kilograms). It was known that the fluid intake was close to two pints (or approximately 1,000 c.c. per day). This figure is close to the requirement necessary for life itself under normal circumstances, and was barely supplemented by the food intake, which was very diminished. The chloride loss through the urine alone represents 2.4 meq. per kilogram per day, or 31 meq. per child per day. It is known that under normal circumstances the loss of chloride from the body as a whole is covered by an intake of only 1.5 to 2 meq. per kilogram per day.* Doubtless additional loss of chloride through the sweat over a prolonged period leads as well, in these children under discussion, to a deficit of total body chloride.

Although direct investigation of the sweat was not undertaken, it is clear from the above that some 70 per cent or more of fluid intake of these children was being lost as "insensible water loss." (Actually, it should under normal conditions account for no more than about 40 per cent.)* We know that alteration of acid-base balance does not appear to modify the composition of the sweat, which is in contrast to the urinary pattern. Evidence is suggestive that alteration of cell tonicity appears to effect the rate of secretion of sweat, but not its composition.[70, 71, 72, 73] In the presence of hypotonicity of the extracellular fluid the rate of secretion of sweat is increased.[72, 73] After the administration of salt there is a diminution of sweating, and the loss of sodium, potassium, and chloride is reduced.[73] The secretion of sweat is important in the process of heat exchange, but apparently it does not play a major role in maintaining homeostasis. It seems that in adrenal insufficiency the loss of sodium and of chloride through the sweat is slightly increased.[74] These electrolytes are decreased in the sweat content in salt depletion.[75, 76] This latter phenomenon, however, depends on the prior development of a negative salt balance, rather than on adaptation to prevent its onset.[76, 77]

There is little or no information in the pediatric literature pertaining to the physiological process of sweating in children, except for the important work done by Cooke, Pratt, and Darrow.[78] For losses of insensible water of the order which has been referred to, these workers showed a loss of 11.3 and 8.8 meq. of chloride per liter of sweat in 14- and 16-month-old infants.

*Darrow, D. C., and Cooke, R. E.: Personal communication.

The concentration of electrolytes in the sweat increases as age progresses. It is much higher in adults (1 to 2 meq. of chloride is lost per kilogram of body weight per day). At temperatures lower than 84° F., one-fourth of the caloric production is dissipated by evaporation of water. When the temperature rises above 84° F., sweating occurs. Above 93° F., all heat loss is by sweating.* The occurrence of noticeable sweating during the Australian summer is therefore not surprising. In winter, sweating must lead to a drop in body temperature or to a rise in metabolism.

Enough has been said to indicate that the fluid loss through the sweat in pink disease is considerable, and the electrolyte losses require study. In Australia the importance of a hot and dry climate cannot be neglected, during the course of pink disease, for sweating is more profuse and prolonged than in any other pediatric condition.

Investigation of the plasma electrolytes in the series of twenty-three cases previously referred to[4, 6] exhibited low plasma sodium and chloride levels. The mean value for the plasma sodium level (124 meq. per liter) shows a deficit of 9 meq. per liter below the lower limit of normal (133 meq. per liter). It was unfortunate that the method used had not previously been adapted to plasma sodium estimations. (This method involved ashing of the plasma and determination by emission spectrophotometry. The measurement of the intensity of the sodium band on a photographic plate was carried out with the aid of a photoelectric galvanometer.) Later work by Williams and his co-workers[79] in Melbourne, while demonstrating a significant deficit of serum chloride in twenty-two cases, and also hemoconcentration, revealed low serum sodium levels in only two cases. Their sodium method employed was by gravimetric analysis, using 0.2 c.c. of serum. It has been the experience of other workers to find a small percentage of lowered serum sodium values in this disease[80]; but the majority of values are normal.[22, 79]

The rise in hematocrit, hemoglobin and plasma protein with normal plasma sodium concentration, or with low concentration, indicates a low plasma volume, and a loss of plasma chloride and sodium.

As a whole, the loss of sodium and chloride in the extracellular fluid in many examples is the same order of magnitude as the loss of plasma volume. However, adequate data are not available to establish the magnitude of the deficit of sodium and chloride in the body as a whole in pink disease. But there is evidence that chloride deficiency may be considerable in some cases. This has also been suggested by therapeutic studies of the use of sodium chloride with and without desoxycorticosterone acetate.[4, 6]

Southby of Melbourne[31] states that "in babies very sick with pink disease there has been a complete absence of hydrochloric acid from the gastric juice." He interprets this as evidence to support the concept that achlorhydria offers easy passage to a hypothetical virus, which possibly causes pink disease. It has been my own observation that cases of pink disease subjected to gastric lavage are liable to collapse and die a few hours later. In the presence of the alarming complication of diarrhea, hypotonic solutions of chloride and sodium demonstrate a

*Darrow, D. C.: Personal communication.

rapidly deleterious effect on the infant with pink disease. Proper attention to electrolyte therapy may be of great value.[4]

The Possible Interpretation of Ionic Changes.—With salt and steroid treatment any small series of cases may show little alteration in the course of this disease,[6] but the spectacular improvement of some patients in this series made it impossible to disregard these results as being purely fortuitous. In retrospect it would seem that any beneficial effect of sodium chloride and/or of desoxycorticosterone to some cases, may rest in the fact that some of the symptoms of pink disease are referable to a chloride deficiency and to hypotonic dehydration. With expansion of blood volume and return of chloride to the body, clinical improvement is often manifest. However, this is not always so (vide below). Because controls were not carried out, the value of this therapy is still open to question.

Alteration of the electrolyte pattern and the above-observed phenomena are further clarified by the data of Williams and his co-workers.[79] Their data show strikingly high serum bicarbonate values. Nineteen out of twenty-two cases were investigated using capillary blood. So high are many of their values (40 meq. or 90 volumes per cent) that individual values are even more significant than the presence of a mean value of 30 meq. per liter. Actually, these workers apparently calculated on the basis of twenty-two cases instead of nineteen, and they obtained a normal mean value. They surprisingly overlooked the significance of their own data. This was pointed out recently.[8]

Neither vomiting nor diarrhea are prominent symptoms to account for this alkalosis. Nor is it likely that sweating per se could produce it. There are many who have championed the thesis that pink disease is due to a disturbance of the central nervous system and/or of the hypothalamus.[31] We are aware of the condition of "cerebral salt wasting,"[82, 83] and other salt-wasting conditions.[84, 85, 86, 87, 88] More recently it has been shown that tuberculous meningitis can give rise to alterations of the plasma electrolytes, not unlike that which is present in the disease under discussion.[82]

In the cases reported by Rapaport and his associates[82] there was impairment of the ability of the kidney either to clear or to conserve chloride in a normal manner. The normal response of a disappearance of chloride from the urine during hypochloremia was absent. In these cases an elevation of plasma bicarbonate was significant, as well as the reduced levels of serum chloride and sodium. In one of the three cases a very low serum potassium level was also apparent, and these authors, being aware of the work of Darrow,[89, 90] realized that "a decrease of the intracellular potassium concentration is an unavoidable correlate of the reduction of the concentration of the extracellular ions."

The presence of significant amounts of chloride in the urine, in the presence of hypochloremia, has been noted in cases of pink disease.[4, 6] To quote but one case, we can consider that of G. C., aged 2 years 8 months.[4] The weight of this child was 10 kilograms. The blood chloride was 425 mg. per cent (normal equals 450 to 500 mg. per cent). Hematocrit equalled 48 per cent and plasma protein 8.1 grams per cent. The twenty-four-hour urine volume was 325 c.c., and contained 2 grams of chloride. She therefore ex-

creted 5.6 meq. of chloride per kilogram per day. This value is remarkably high (as mentioned in other cases cited previously) and was at a time when fluid intake was minimal.

The electrolyte disturbance in pink disease is most likely related to an alteration of the renal regulation of acid-base equilibrium augmented by electrolyte losses in the sweat.

First one should consider that anorexia being marked, the intake of potassium must be very low. In animals low intake of potassium combined with high intake of sodium chloride can produce marked alkalosis, and this deficit of potassium leads to a loss of chloride.[89, 90] Second, and this would seem even more relevant, deficit of chloride can lead to a loss of cellular potassium.[89, 90] Cellular potassium deficiency is not necessarily characterized by a fall in serum potassium. Some of the serum values in pink disease are low (3 meq. per liter).[79]

Darrow was able to demonstrate by animal experiment that in alkalosis produced by depletion of chloride, the serum potassium concentration is low or normal. Muscle potassium is low, and intracellular sodium is high. The loss of intracellular potassium occurred despite abundant potassium in the diet. It was suggested therefore that during clinical alkalosis there was an intracellular loss of potassium and an increase in cellular sodium in the presence of normal renal function.[90]

Later work involving induced deficits of chloride, sodium, and potassium ions, respectively, showed a high degree of correlation between the concentration of bicarbonate in the serum, muscle potassium, and intracellular sodium. Serum bicarbonate varied directly with intracellular sodium and inversely with muscle potassium. Muscle potassium and intracellular sodium showed inverse relationships. It was considered that the existing ionic relations could be regarded as a biological equilibrium which is attained when renal adjustment is made in the presence of a deficit of sodium, of chloride, or of potassium.

More recent work in which I have been concerned[91] more adequately defines these relationships and reveals important facts. This particular study of tissue and renal adjustment to single ion deficiencies has produced considerable data and information previously not anticipated. A large series of rats were rendered potassium deficient, and alkalotic. These animals were then divided into two groups. The first group (K) was given potassium chloride, 3 millimols per kilogram, twice a day, by injection for one week. Group 2 (Na) received 3 millimols of chloride (as sodium chloride) in the same way and dosage. Urine, blood, and tissue analyses were undertaken before and during this therapy. The group Na animals demonstrated some renal compensation for the alkalosis by excreting urine of a high pH and low titratable acidity. The group K animals excreted urine of low pH, high titratable acidity and a high ammonia content. The urinary bicarbonate values closely followed the pH in both groups. Despite the absence of a renal compensatory mechanism in the group K animals, at the end of one week the extracellular alkalosis was corrected, and muscle composition was normal. On the other hand, although in the group Na animals there was some renal compensation for alkalosis, at the end of one week it was found, by serum analysis, to be aggravated, and muscle composition was

shown to be grossly abnormal with respect to intracellular electrolytes.

Obviously, then, in alkalosis and potassium deficiency the administration of potassium leads to correction of the ionic changes by exchange of ions between the extra- and intracellular phase. This is an extrarenal occurrence. During potassium deficiency and alkalosis sodium replaces potassium inside the cells, but there is not complete reciprocity between these cations. Only about two-thirds of the potassium is replaced by sodium. If, then, administration of potassium can bring about ionic equilibrium, it is clear that unless there is some radical change of ionic structure within the cell itself, there is approximately one-third of the lost potassium cations to be accounted for. Thus, the evidence is suggestive that hydrogen ions as well as sodium ions enter the cell to replace potassium; and during correction of the induced alkalosis, hydrogen ion moves out of the cell along with sodium, to restore equilibrium. Thus, this study has shown again the importance and necessity of giving potassium in clinical alkalosis. It also reveals the extrarenal manner in which potassium restores ionic equilibrium.

It has been known clinically that sodium chloride is of benefit in many cases of alkalosis. It is also known that this is not so under all circumstances (i.e., when cellular potassium deficits are present).

With respect to pink disease, the above research is important, for the data of Williams and his co-workers[79] draw attention to metabolic alkalosis of a significant duration. Their data offer a definite challenge for further elucidation of the behavior of the electrolytes, sodium, potassium, and chloride. Provided their determinations are accurate, they confirm beyond doubt the presence of an electrolyte disturbance, and reveal an acid-base imbalance.*

It should be pointed out that if cellular potassium depletion exists in pink disease, this could well explain the variability of therapeutic results observed after giving sodium chloride.

It is of interest to refer back thirty years ago to the early paper of Brown, Courtney, and MacLachlan from Toronto,[13] which contains the only complete and single metabolic studies in the literature. Metabolic investigations on a 3-year-old girl, receiving a reasonable caloric intake of 75 calories per kilogram, showed (recalculated in modern terms) a negative balance for potassium (1.104 meq. per day), for sodium (0.135 meq. per day), and for nitrogen (0.158 gram per day). Ninety-eight per cent of the sodium and nitrogen loss occurred through the urine, and 94 per cent of the potassium loss. Sweating was neglected. When one considers this, and also the duration of the disease, these values may well be significantly large over a long period.

Attention has recently been directed to alkalosis resulting from mercurial diuretics.[92] Here chloride is said to be excreted in excess of sodium. In view of the work of Warkany,[23] this aspect also obviously requires elucidation.

Clearly, our knowledge of the altered electrolyte pattern in pink disease is as yet incomplete, and to some extent in this paper speculation has been entertained. The magnitude of chloride, sodium, and potassium loss must be determined, the role of mercury clarified, and the nature of the disturbance of renal function and acid-

*Darrow, D. C.: Personal communication.

base imbalance defined in terms of modern concepts.

Restoration of homeostasis by appropriate electrolyte therapy in states of prolonged ionic disturbance, such as the interesting and contrasting conditions of "renal acidosis,"[93] can go far toward neutralizing the undesirable effects of disease.

SUMMARY

A. The history of pink disease has been briefly reviewed and the known facts concerning and surrounding its incidence are recorded. On the basis of experience, and close study of over 100 cases, a description of the symptomatology is given from the viewpoint of the manifestation of this disease in (1) infants and (2) older children.

B. Modern etiological concepts are reviewed with special reference to (1) the role of mercury, (2) the nervous child and psychological factors, (3) the autonomic nervous system, (4) the adrenal gland. The role of the adrenal gland (cortex and medulla) has been investigated and evaluated from all aspects. Attention to the importance of "stress" has been originally described and discussed.

C. A physiological approach to this disease is presented and advocated. From such an approach the following points have so far been determined or suggested:

1. In pink disease there is a depletion of chloride and sodium ions in the vascular space; neither the chloride nor the sodium ions rise concomitantly with the existing hemoconcentration.

2. There is some contraction of the blood volume and some loss of water from the blood stream. We are apparently dealing with extracellular hypotonic dehydration.

3. There is a significant and surprising amount of water loss as "insensible water loss." There is probably appreciable loss of electrolyte through the sweat glands.

4. There is evidence that the kidneys are excreting significantly high amounts of chloride—more than can be ascribed to intake.

5. The existence of alkalosis has been pointed out, and the possibility of cell potassium deficit as a sequel or chloride depletion is presented. The use of sodium chloride therapeutically may be of value in some cases. The question is unsettled.

6. Evidence is suggestive of an alteration of blood pigment metabolism in this disease. This is suggested by the presence of free oxyhemoglobin in the plasma, and a slightly raised coproporphyrin excretion. The state of the capillaries has been defined by direct microscopy, and reference to the vascular system has been made in terms of the available evidence.

7. The above electrolyte changes throw some light on the understanding of this disease, and there is reason to believe that further attention to electrolyte disturbance and deficits of chloride, sodium, and potassium will lead to further and more clearly defined therapeutic aids.

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ADDENDUM

Recently a patient with infantile acrodynia, 19 months of age and weighing 9.43 kilograms, was admitted to the Hospital for Sick Children, Toronto,* and came under the care of this author. The typical history extended over a period of four weeks and questioning revealed that a mercurial medication had been used three months previously for the treatment of "impetigo." Examination of the child supported the history. Investigations revealed the following: serum Na, 135 meq. per liter; serum Cl, 103 meq. per liter; serum K, 5 meq. per liter; serum pH, 7.48; serum bicarbonate, 21.6 meq. per liter; hematocrit, 45 vol. per cent; hemoglobin, 15 grams per cent; plasma protein, 7.10 grams per cent; nonprotein nitrogen, 47 mg. per cent; white blood count, 12,700 (with a normal differential count); absolute eosinophil, 170 cells; blood pressure, 135/105. The electrocardiogram showed inversion of the "T waves" in the precordial leads. The weight was 9.43 kilograms. The urine was noticeably charged with urates and showed specific gravity values which ranged from 1.033 to 1.037. The pH of the urine on the first day was 6.4 and this value steadily increased. All urine specimens showed a positive test for ketones and occasionally showed the presence of a trace of sugar or albumin. The plasma volume (using the dye T 1824) was 350 c.c. (30 per cent reduction). The extracellular water (using a bromide space method which I developed[66]) was found to be 16 per cent of the body weight. The normal value found with this method for adults is 20 per cent and for infants it is probably higher. As the bromide space is a measure of total body chloride, this result indicates a deficit of the chloride ion.

According to the mother the child had lost 5 pounds in four weeks and refused all foods except milk and clear fluids. In hospital she was placed on a milk diet together with "sugar solution" and vitamins. In the first ten days an effort was made to study the fluid and electrolyte balance. The fluid intake, which only amounted to some 500 c.c. per day, was analyzed and likewise the urine and feces excreted. Twenty-five per cent of the fluid intake was lost as scanty concentrated urine. Some 75 per cent of fluid intake was therefore lost as sweat and as insensible water loss. The stools were very small and constipated. The caloric intake was of the order of 35 calories per kilogram per day. During the first ten days in hospital it was possible to make only four complete twenty-four-hour urine collections. However, analysis of the urine alone with respect to intake showed a negative balance for Na, Cl, and K, and the loss of Na and Cl was greater than the loss of K. The mean of the values for urinary electrolyte excretion indicated a daily net loss of 3 meq. of Na, 2 meq. of Cl, 1.5 meq. of K, and 0.7 gram of nitrogen. Correction for stool electrolyte loss showed a net daily deficit of 3.5 meq. of Na, 2.6 meq. of K, 2.9 meq. of Cl, and 0.86 gram of nitrogen per day.

This loss of electrolyte from the body and the electrolyte changes tak-

*Present location of the author.

ing place were emphasized by the blood investigations performed on the eleventh day: serum Na, 130 meq. per liter; serum Cl, 93 meq. per liter; serum K, 4.6 meq. per liter; serum pH, 7.55 (repeated twice); serum bicarbonate, 26.5 meq. per liter; hematocrit, 43 vol. per cent; nonprotein nitrogen, 39 mg. Electrocardiogram: abnormal tracing the same as previously. The urine pH equalled 7.6. The weight fell to 9 kilograms.

On the twelfth day the patient was given a liter of milk which contained 10 Gm. of sodium chloride and 2 Gm. of potassium chloride. Much to the surprise of the nursing staff this feeding was readily taken, and almost gone before the end of the day. The urinary balance for that day showed a retention of 28 meq. of Na and 61 meq. of Cl and no gain or loss in K.

On the thirteenth day only sugar solution was taken without the addition of electrolyte, and during this twenty-four-hour period the urine showed a net loss of 53 meq. of Na, 6.5 meq. of K, and 49 meq. of Cl.

On the fifteenth day blood investigations showed: serum Na, 135 meq. per liter; serum K, 5.0 meq. per liter; serum Cl, 95.5 meq. per liter; serum pH, 7.52; serum bicarbonate, 20.5 meq. per liter; nonprotein nitrogen, 32 mg.

The patient was then given sugar solution only, which contained 4 Gm. of sodium chloride (68 meq.) and 5 Gm. of potassium chloride (67 meq.) per liter. This solution was well taken over a continuous period. Some improvement was noticed in the child's clinical condition. At the end of the first twenty-four-hour period urinary balance showed a retention of 15.6 meq. of Na, 8.3 meq. of K, and 32 meq. of Cl. At the end of the second twenty-four hours there was a further retention of 10.9 meq. of Na, 3.8 meq. of K, and 10.5 meq. of Cl. The caloric intake was 35 calories per kilogram per day and the fluid intake 620 c.c. per day. At this time the electrolyte levels were: serum Na, 138 meq. per liter; serum Cl, 104 meq. per liter; serum K, 4.55 meq. per liter; serum pH, 7.55; serum bicarbonate, 22.4 meq. per liter; nonprotein nitrogen, 24 mg.

The venous pressure of this child was measured during sleep produced by sedation. This was found to be surprisingly high: 203 mm. of water (above the right auricle). The upper limit of normal is 120 mm. The urine contained 0.06 mg. per liter of mercury. 17-Ketosteroid excretion was 0.68 mg. (as androsterone).

Briefly, from these investigations it is clear that there is, in this case, an excessive loss of electrolyte from the body, mainly through the kidney. That there is an excessive loss of sodium through the kidney under conditions approximating semistarvation is interesting, as conservation of sodium is an outstanding requirement in the regulation of fixed base excretion during fasting if the integrity of extracellular fluid volume and of the blood volume is to be preserved. Presumably there is also a significant deficit of the chloride ion and perhaps the rise in the urinary pH is a reflection of the method employed by the kidney to try to conserve the chloride ion. The rise in serum pH must account for increased cell potassium loss over and above that due to starvation and also for the entrance of sodium and hydrogen ion into the cell.[91] It is of interest that the presence of ketones in the urine, and presumably in the blood, was constant and under usual circumstances would have led to acidosis.

This state of inanition, of hypotonic dehydration, and of alkalosis as depicted here could well be ascribed to kidney tubular damage occasioned by the effects of some toxic agent such as mercury.

Indeed, as a basis for further investigation one might speculate as follows. We may have here the picture of a relentless sodium and chloride diuresis due to mercury and most of the altered physiology in this disease might find explanation on this basis. The raised venous pressure and most likely a reduced kidney glomerular filtration rate are all recognized adjustments which tend to prevent elec-

trolyte loss due to mercurial agents. This has been shown in cardiac cases.[94]

The reason for high urinary concentration would thus become apparent as a necessary saving of electrolyte with the overworked sweat glands assuming the role of a poor kidney to deal with the excretion of water and the conservation of salt. Increased cellular hydration with a shift of water from the extracellular space, leading to cerebral edema, is a logical explanation for irritability, insomnia, and photophobia. The muscle weakness is possibly due to cell potassium deficiency P; and the manifestations in the extremities are perhaps due to arteriolar spasm and stagnant anoxia. Likewise the blood pressure could be the result of a generalized reflex arteriolar spasm. The tachycardia could result from the increased load placed on the cardiovascular system, and in the presence of a diminished blood volume, the left ventricle would be hard pressed to maintain a sufficient cardiac output.

Initially, the kidney might excrete more chloride than sodium and the resulting alkalosis would offset to some extent the mercurial effect on the kidney tubule. The ingestion of mercury at a period when the infant or young child is growing rapidly might facilitate the deposition of this metal in the bones and elsewhere in some complex form, only to be slowly and relentlessly liberated at some later date. The presence of cell potassium deficiency would explain why these children quickly die, if gastroenteritis arises as a secondary complication. This disturbance of electrolyte and water metabolism would place the adrenal gland under stress and would account for an increased excretion in adrenal hormone.

From recent work it is apparent that one hormone which is effective against such mercurial action on the kidney is desoxycorticosterone acetate (ACTH).[94]

The case presented developed diarrhea (hemoconcentration increased), which yielded quickly to the administration of continuous normal saline with plasma and oral KCl. Hypotonic solution did not establish hydration. Subsequently 6 Gm. of NaCl and 3 Gm. of KCl were given in the oral fluids with 2 mg. of DCA by injection. After one week of this regime, irritability, anorexia, insomnia, and inertia disappeared. Forty-eight-hour balance studies (urine and feces) then revealed a daily retention of 36 meq. of Na, 15 meq. of K, 58 meq. of Cl, and 0.5 Gm. of nitrogen. Serum pH was now normal, the hematocrit fell to 41 vol. per cent and serum Na remained at 135 meq. After two weeks of DCA this was discontinued and three days later serum electrolytes were normal and the plasma volume was 475 c.c. The extracellular water had risen to 29 per cent of the body weight. The venous pressure was 165 mm. The electrocardiogram showed that the inversion of the T waves, in the precordial leads, had diminished.

Psychologic Aspects of Pediatrics

THE TREATMENT OF BEHAVIOR DISORDERS IN CHILDREN WITH BENADRYL

A Preliminary Report

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THE use of drugs in psychiatry either as a research tool or as a therapeutic weapon has not been adequately emphasized. Recently, Dr. Karl Menninger,[1] in discussing research in psychiatry, pointed out that drug experimentation is a developing but insufficiently investigated field. He further stated, "It is regrettable that while physiological and neurological studies for a long time dominated psychiatric research with a phenomenological aim, drug investigations so much related to the physiological investigations have been undoubtedly neglected." In his review of child psychiatry in 1952, David Levy[2] emphasized the "value and promise" of pharmacological research.

Evaluation of drug therapy in psychiatric disorders of children has been mainly confined to compounds of the amphetamine and hydantoin groups. Bradley and Bowen[3] in 1941 treated 100 children with Benzedrine Sulfate. Fifty-four per cent became "physically and emotionally, but not intellectually" subdued, 19 per cent were stimulated to better integrated and useful behavior, 21 per cent were unaffected, and 7 per cent retrogressed. The only group that showed no improvement were those with structural defects of the brain. Subsequently, Bradley[4] reported similar results with Dexedrine Sulfate. Bender and Cottingham[5] reported an over-all improvement in behavior and relationships in 58 per cent of cases treated with Benzedrine. There was marked improvement in cases diagnosed as psychoneurotic and neurotic behavior disorders. However, no improvement was noted in those cases diagnosed as psychopathic personality, schizophrenic, or organic.

Several groups of investigators have evaluated the effectiveness of the hydantoin compounds in child behavior disorders. Most of the children studied were known to have abnormal electroencephalograms. Brown and Solomon[6] used Dilantin Sodium. They reported improvement in three of seven delinquent children with serious behavior problems and abnormal electroencephalograms characteristic of psychomotor epilepsy. A similar study by Walker and Kirkpatrick[7] showed more encouraging results. Of ten children with behavior problems and abnormal electroencephalograms, all showed improvement with Dilantin Sodium.

More recently, Pasamanick,[8] with the aid of several independent observers, carefully studied twenty-one children with psychiatric disorders. Fourteen of the children were diag-

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nosed as primary behavior disorders. The remaining seven children had other psychiatric diagnoses, but none of them was considered to be schizophrenic. All of the twenty-one children were found to have abnormal electroencephalograms. Several drugs were administered. The effectiveness of anticonvulsant medication was uniformly disappointing. Only one child showed a beneficial result with Dilantin Sodium. This same child also improved with Mesantoin; in another child there was questionable improvement with Mesantoin. Of nine children who received Tridione, only one was benefited. Phenobarbital was administered to six children. One child showed marked improvement, and one slight improvement. With amphetamine, four of ten children had marked or unequivocally beneficial results. Pasamanick concluded that amphetamine was the only one of the drugs he evaluated which could be considered of therapeutic value in the treatment of child behavior disorders.

We[9, 10, 11] have observed and evaluated the usefulness of several medicaments in organic diseases of the central nervous system, and in adult psychiatric disorders. Since the pharmacological approach to child psychiatry seemed promising, we initiated a clinical investigation into the effectiveness of these and related compounds on the Children's Psychiatric Ward of Bellevue Hospital. A screening procedure was established to briefly evaluate the possible effectiveness of these drugs, and it was intended that those drugs which seemed to be most beneficial would be subjected to a more complete and carefully controlled investigation. This report is the result of preliminary observations with Benadryl.*

PROCEDURE

Forty-four unselected children with psychiatric disturbances were treated with Elixir Benadryl. This group of cases consisted of thirty-four male and ten female children who ranged between the ages of 6 and 12 years. Of these forty-four children, twenty were diagnosed as schizophrenic, thirteen were organic, eight were primary behavior disorders, two were psychopathic, and one was mentally defective. The children were chosen at random at the time of their hospital admission. They were not treated differently from other children on their ward. Since many of the children received medication this test group was not particularly differentiated in this respect. However, in the final series comparisons will be made with children receiving placebo identical to the active drug. The children were first observed on the ward for ten to twenty-one days, until they were thought to have arrived at a relatively steady state of behavior. Then they were given increasing doses of Benadryl for a period of four weeks. After the administration of the drug was discontinued, observation was maintained until the child was discharged from hospital. Evaluations were recorded by members of the staff, i.e., house staff psychiatrist, research staff psychiatrist, nursing staff, schoolteachers, recreation instructors, and psychologists. Changes were recorded for the following categories:

1. Excessive motor activity.
2. Anxiety.

*The Elixir Benadryl was kindly supplied by Parke, Davis & Company, Detroit, Mich.

3. Relationship problems with other children.

4. Relationship problems with adults.

5. Soft neurological signs.

6. Affect.

7. Pathognomic symptomatology and fantasy life, i.e., introjected bodies and hallucinations.

In addition, each child had an electroencephalogram before and at the end of the four-week period of drug therapy. Bender-Gestalt tests, Good-enough drawings, and free drawings were also collected before and during treatment. Improvement or aggravation of symptoms was indicated by each observer with plus or minus signs. If any one of the above categories was not considered to be significant for a particular case, it was so indicated, as shown in Table I. To prevent slight changes from unduly influencing the results, the following 5-point scale was adopted:

++: Marked improvement.
+: Moderate improvement.
0: None or slight change.
−: Moderate aggravation.
−−: Marked aggravation.

The dosage schedule of the Elixir Benadryl was as follows:

First week: 10 mg. 3 times a day.
Second week: 20 mg. 3 times a day.
Third week: 30 mg. 3 times a day.
Fourth week: 30 mg. 4 times a day.

RESULTS

Results are indicated in Tables I, II, and III.* As can be seen in Table I, 61 per cent of the cases showed improvement in at least one category, 34 per cent showed no improvement, and 5 per cent showed aggravation of symptoms. Of those cases that did show improvement, 49 per cent improved in three to five categories, and only 12 per cent in one or two categories. None of the children showed any significant change in the soft neurological signs or in pathognomic symptomatology and fantasy life. Comparative evaluation of the individual categories indicated that anxiety symptoms and relationship problems with adults were most benefited. A reduction in manifest anxiety occurred in 54 per cent of the cases; and an improvement in the child's relationship problems with adults was found in 56 per cent of the cases. Forty-four per cent of the children showed improved relationship with their peers. In those cases in which depression was the prevailing mood,

TABLE I. PER CENT OF ALL CASES SHOWING IMPROVEMENT IN EACH CATEGORY WITH TREATMENT BY BENADRYL

	IMPROVED	NORMALITY MAINTAINED*	UNIMPROVED	AGGRAVATED
Hyperactivity	29	20	49	2
Manifest anxiety	54	2	42	2
Relationship problems to peers	44	0	51	5
Relationship problems to adults	56	0	39	5
Depressed affect	37	0	63	0

	IMPROVED	AGGRAVATED
Three to five categories	49	2+
One to two categories	12	2+
No categories	34	−

	SOME IMPROVED	UNIMPROVED	SOME AGGRAVATED
All cases	61	34	5

*Those cases in which the category was not significant.

*Statistical analysis was done by Mr. William Helme.

37 per cent benefited by elevation of mood. Of those children who were hyperactive during the preliminary observation period, there was a reduction of this hyperactivity in 29 per cent with Benadryl.

ment with Benadryl. The older schizophrenics, i.e., those between the ages of 9 and 12 years, appeared to improve in larger numbers than the younger ones. By taking the mean number of improved categories, it

TABLE II

PER CENT OF CASES IMPROVED WITH BENADRYL TREATMENT BY AGE AND DIAGNOSIS

	AGES 6-8 YEARS			AGES 9-12 YEARS		
DIAGNOSIS	CASES	IMPROVED	NOT IMPROVED	CASES	IMPROVED	NOT IMPROVED
Schizophrenic	6	33	67*	15	60	40*
Organic	7	43	57	6	50	50
Behavior disorders	0	–	–	8	100	0

MEAN NUMBER OF IMPROVED CATEGORIES WITH BENADRYL TREATMENT

	AGES 6-8 YEARS		AGES 9-12 YEARS	
DIAGNOSIS	CASES	MEAN IMPROVEMENT†	CASES	MEAN IMPROVEMENT†
Schizophrenic	6	.89	15	2.01
Organic	7	2.14	6	1.67
Behavior disorders	0	—	8	3.47

PER CENT IMPROVED AND MEAN IMPROVEMENT WITH BENADRYL TREATMENT DIAGNOSTIC GROUPINGS ALONE

DIAGNOSIS	CASES	PER CENT IMPROVED	MEAN IMPROVEMENT
Schizophrenic	21	52	1.70
Organic	13	46	1.92
Behavior disorders	8	100	3.47

*Includes one case showing aggravation.
†Aggravated case entered as minus one.

TABLE III

PER CENT OF CASES IMPROVED WITH BENADRYL TREATMENT BY I.Q. AND DIAGNOSIS

	I.Q. UNDER 80			I.Q. 80 AND OVER		
DIAGNOSIS	CASES	IMPROVED	NOT IMPROVED	CASES	IMPROVED	NOT IMPROVED
Schizophrenic	13	69	31	6	17	83*
Organic	6	17	83	6	67	33
Behavior disorders	2	100	0	6	100	0

MEAN NUMBER OF IMPROVED CATEGORIES WITH BENADRYL TREATMENT

	I.Q. UNDER 80		I.Q. 80 AND OVER	
DIAGNOSIS	CASES	MEAN IMPROVEMENT	CASES	MEAN IMPROVEMENT
Schizophrenic	13	2.66	6	–.71†
Organic	6	.83	6	2.50
Behavior disorders	2	3.50	6	3.46

*Includes two cases showing aggravation.
†Aggravated cases entered as minus one each.

Table II represents a breakdown according to age and diagnosis. It can be seen that of the eight children who were diagnosed as primary behavior disorder, all showed improve-

would appear that in the younger age group, i.e., from 6 to 8 years, the organic behavior disorders showed greater improvement than the schizophrenics. This difference disappears

in the older age group. The over-all improvement in the behavior disorders is reflected in a mean number of 3.47 in improved categories. When one groups all the cases together according to diagnosis, there is no significant difference between the schizophrenics and the organics, while those with behavior disorders do best of all.

The data were studied in terms of intelligence quotient (Wechsler Intelligence Scale for Children) and diagnosis (see Table III). According to these data schizophrenic children with I.Q.'s over 80 showed the most marked improvement. All of the children with behavior disorders showed improvement. This observation is again reflected when the mean number of improved categories is listed against the intelligence quotient. Analyses of Bender-Gestalt tests, drawings, and electroencephalograms made before and during administration of Elixir Benadryl will be presented in a later communication.

DISCUSSION

It would appear from this preliminary study that Benadryl is a useful drug in controlling the manifest symptomatology of children with psychiatric disorders. This therapeutic effectiveness is indicated in the statistical breakdown, and it compares favorably with the reported beneficial effects of the amphetamine group of drugs. Bradley reported improvement in 72 per cent of his cases who received Benzedrine, while Bender and Cottingham reported an over-all improvement of 58 per cent in their group. Pasamanick obtained benefit in 40 per cent of his cases with Benzedrine, whereas 61 per cent of our cases showed some degree of improvement with Benadryl.

Clinically, Benadryl appears to be most satisfactory in the therapy of primary behavior disorders, especially in those patients who show considerable manifest anxiety. The major therapeutic usefulness of Benadryl seems to be its effect in reducing anxiety and, at the same time, improving relationship problems to significant adults. To a lesser degree it improves relationships with peers. No explanation can be given for the improvement in the low I.Q. schizophrenic and the high I.Q. organic cases. However, the entire clinical picture and areas of improvement may be better understood after investigations in progress at the present time are completed. In these further investigations some children receive placebo medication while other children simultaneously receive active medication. In this manner changes in behavior in a child receiving drugs can be compared with a child not receiving drugs. Some of the beneficial results recorded might be part of the general trend of improvement seen in the ward population. However, this study does suggest that not all the improvement can be ascribed to hospital confinement. Such improvement surpasses that which is ordinarily seen in untreated patients, or in patients receiving phenobarbital.

While the drug may not alter the entire course of the disturbance, it has been found to be of definite benefit. However, as has been pointed out, the precise nature of the improvement will be better discernible when control studies have been completed.

In addition, it has been observed that in certain acutely disturbing situations a number of children will definitely benefit from the administration of Elixir Benadryl. Thus, children with sleep disturbances, especially night terrors, seem to obtain a rapid relief from symptoms with a general improvement in behavior.

It should be noted that no toxic symptoms were evidenced in any of the children from the administration of Elixir Benadryl. The maximum dose administered to any child was 160 mg. a day. Only one boy, who was diagnosed as a behavior disorder due to diffuse organic brain disease, displayed sleepiness. All the other children were alert while receiving drug.

SUMMARY

1. Elixir Benadryl was administered to forty-four children with behavior disorders.

2. Sixty-one per cent of the patients showed some improvement.

3. Children with primary behavior disorders, especially those with manifest anxiety, were most benefited.

4. Benadryl is of value in the treatment of certain acutely disturbing situations in children.

5. No toxic symptoms were observed in children from the administration of Elixir Benadryl.

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Comments on Current Literature

ENCEPHALOMYOCARDITIS

ASSOCIATED inflammation of the central nervous system and of the myocardium has been observed in poliomyelitis with some degree of frequency. But when the latter disease is excluded, concurrent involvement of the brain and the heart on a viral basis is considered of rare occurrence. In the December, 1952, issue of *Circulation,* Otto Saphir[1] describes three cases which from the standpoint of clinical findings and pathologic studies fall into the category of encephalomyocarditis. Saphir's report comprises a review of this clinical and pathologic entity, together with the results of complete pathologic studies on all three of his patients.

Although Fiedler in 1899[2] reported a series of cases of acute interstitial myocarditis, one of these patients apparently showing some encephalitic involvement, the concept of encephalomyocarditis as an entity, possibly on the basis of virus infection, did not gain impetus until 1945, when Helwig and Schmidt[3] described enlightening experimental work in this field. These investigators observed a clinical entity occurring in apes which was characterized by diffuse interstitial myocarditis, bilateral hydrothorax, and pulmonary edema. A filtrable agent was isolated from the chest fluid of apes infected with this disease, which produced myocarditis in guinea pigs, and paralysis and widespread myocarditis in mice and hamsters. Warren and Smadel,[4] who carried out further investigations with this infectious agent isolated from apes, were able to demonstrate that the agent became highly neurotropic for mice on serial intracerebral passage. In mice which succumbed rapidly to the disease, Warren and Smadel found no microscopic evidence of myocarditis, but when the infection progressed more slowly and death was delayed, an extensive, focal, necrotizing myocarditis occurred, which was readily recognizable grossly. This newly isolated viral agent was designated EMC virus (encephalomyocarditis), and on further study, neutralization, cross immunity, and complement fixation tests[5] revealed a close immunologic relationship between the EMC virus and the Columbia SK and MM strains of meningoencephalitis virus. Likewise, the pathogenicity and pathogenesis of these strains in experimentally infected small animals seemed to be completely comparable.

Saphir, in reviewing the findings in his three patients with encephalomyocarditis, was impressed with the similarity between the disease process in human subjects and that described in apes. His first patient, a woman, 52 years of age, presented a clinical picture characterized by headache, fever, generalized convulsive seizure, auricular fibrillation, and increasing stupor. Pertinent laboratory studies included examination of spinal fluid, which showed the presence of traces of globulin and a pleocytosis of thirty cells, 50 per cent of which were lymphocytes, and an electrocardiogram which was interpreted as abnormal, but was not considered typical of any specific heart lesion.

Pathologic studies which were carried out in detail revealed perivascular round-cell infiltration and perivascular hemorrhage in the central nervous system, as well as degenerative changes in the ganglion cells. At autopsy the myocardium was described as flabby in tone, and in color, brown tinged with yellow. On microscopic examination the myocardial muscle fibers appeared swollen, and considerable accumulation of large mononuclear cells and lymphocytes was observed in the interstitial tissues.

The second case reported by Saphir was that of a man, 35 years of age, whose short clinical course was characterized by severe headache and fever. Death, which occurred one week after onset, was sudden and unexpected, following within a short time after the patient first sought the advice of a physician. A study of autopsy material showed the presence of degenerative changes in the ganglion cells and focal infiltration of round cells and polymorphonuclear leukocytes in the brain. An interstitial myocarditis was observed which was characterized for the most part by degeneration and necrosis of muscle fibers.

The third case, a boy of 13 years, was admitted to the hospital because of convulsions. At the time of admission, about one week following an indefinite onset, the patient was comatose, febrile, and was having increasing respiratory difficulty. He died seven hours following arrival at the hospital. Pertinent laboratory studies included examination of the spinal fluid, which revealed no abnormalities, and urinalysis which indicated the presence of four-plus albumin. On post-mortem examination striking enlargement and dilatation of the heart was noted. Microscopic pathology included interstitial myocardial infiltration by round cells, degeneration of heart muscle fibers, and degenerative changes in the ganglion cells of the central nervous system. In addition to these findings, interstitial pneumonitis and acute intercapillary glomerulonephritis were described.

On the basis of the clinical and pathologic findings in these three patients, Saphir concluded that each had had concurrent encephalitis and myocarditis, and that these cases presented features similar to those of the encephalomyocarditic entity which had been described in apes. The occurrence of encephalomyocarditis in man and the possible relationship between this condition in the human subject and that observed in apes is supported somewhat by further investigative work of Smadel and Warren[6] who demonstrated neutralizing antibodies to the encephalomyocarditis virus in serum specimens collected from military personnel who were recuperating from a short febrile illness contracted in the Philippines. In this instance the clinical course observed was not so severe as that described by Saphir. The illness as observed in soldiers from the Philippines was a rather mild disease, characterized by fever, meningeal signs, pleocytosis of 50 to 500 cells, majority, lymphocytes, and followed by recovery without sequelae in four to five days. Whether this disease process represents a milder form of the more fulminating illness described by Saphir is a question the answer to which must await further study. At any rate, the presence of detectable humoral antibody to EMC virus constitutes presumptive evidence of infection, or casual encounter, with some agent similar, at least immunologically, to this strain of encephalomyocarditis virus.

While Saphir was not in a position to present definite information concerning the etiology of the disease in his three patients, he was able to conclude in each instance that the patient did have acute encephalitis associated with acute myocarditis. In the interest of gaining more information concerning this interesting clinical entity, this author urges that appropriate viral studies be undertaken in the case of patients who present signs and symptoms of central nervous system and heart involvement. When patients are observed who fall into this clinical category, it would be advantageous to secure body fluids for possible demonstration of type-specific antibodies to known strains of virus, especially the demonstration of increasing titer of antibody during clinical recovery. Likewise, isolation of the infectious agent should be attempted by appropriate inoculation of suitable laboratory animals. When autopsy permission is granted, plans should be made for the selection of appropriate tissue specimens, taken under proper conditions, for the express

purpose of animal inoculation. In this respect, close collaboration between the clinical staff and laboratory personnel is essential, and may yield results which will serve to throw light on such an interesting syndrome as that described here, i.e., concurrent encephalitis and myocarditis.

RUSSELL J. BLATTNER.

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News and Notes

The following were certified by the **American Board of Pediatrics,** at the examination at Boston, Mass., Dec. 5, 6, and 7, 1952.

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A new quarterly review published in French and English was started in 1952, sponsored by the International Children's Centre in Paris. The title is *Neo-natal Studies* or *Etudes Neo-natales*. Three Americans interested in the newborn are on the editorial staff: Drs. Henry Barnett, Edith Potter, and Clement A. Smith. Those interested may obtain detailed information as to the journal from the International Children's Centre in Paris.

The **Committee on Rheumatic Fever and Cardiac Disease** of the **American Academy of Pediatrics** has arranged for two three-day courses on rheumatic fever and rheumatic heart disease for pediatricians with emphasis on the clinical aspects of the disease.

New York: New York University Postgraduate Medical School, April 15, 16, and 17, 1953, daily 9:00 A.M. to 4:00 P.M. Minimum enrollment 8, maximum 16. *Wednesday, April 15:* Bellevue Hospital—Drs. Currier McEwen, Ann Kuttner, L. Sokoloff, Janet Baldwin, and Katherine Brownell. *Thursday, April 16:* Irvington House—Dr. G. H. Stollerman and staff. *Friday, April 17:* University Hospital—Drs. J. S. Butterworth and M. M. Maliner. For information as to fee and enrollment address Dr. C. E. delaChapelle, Associate Dean, N. Y. U. Postgraduate Medical School, 477 First Ave., New York 16, N. Y.

Philadelphia: University of Pennsylvania Medical School, The Children's Hospital of Philadelphia, April 24, 25, and 26, daily 9:00 A.M. to 5:00 P.M. Enrollment limited to 10. *Friday, April 24*—Drs. Rachel Ash, Sidney Friedman, and John Hope. *Saturday, April 25*—Drs. S. Friedman and Rachel Ash. *Sunday, April 26*—Drs. Sidney Friedman, Harvey N. Vandegrift, John P. Hubbard, and T. N. Harris. For information as to fee and enrollment address Dr. Rachel Ash, Associated Professor of Cardiology in Pediatrics, The Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.

An intensive course on "Practical Aspects of Common Endocrine and Metabolic Disorders of Children and Adolescents" will be given by Dr. Nathan B. Talbot and associates under the auspices of the **Harvard Medical School** at the Massachusetts General Hospital on April 16 to 18, 1953, which are the three days immediately preceding the Boston meeting of the American Academy of Pediatrics. Those interested should write to the Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass. Attendance will be limited.

Book Reviews

Brain Surgeon. The Autobiography of Dr. William Sharpe. New York, 1952, The Viking Press, 271 pages. Price $3.75.

The reviewer has found a large part of Dr. Sharpe's autobiography both interesting and amusing. His picture of the life and work of the medical student of fifty years ago will arouse the memories of all the "old-timers." It is something quite different from the present-day life. His anecdotes of his association with some of the medical leaders of past years, as Harvey Cushing, are most interesting in showing the personalities of these men. Dr. Sharpe's Chinese experiences sound like a good short story in a fiction magazine. Naturally in a medical autobiography considerable attention is paid to the author's own medical interest and work. This is of lesser interest in this particular story as not all of Dr. Sharpe's surgical ideas have received general acceptance. As a whole, the autobiography is well worth reading as it gives an interesting personal picture of medical education and practices not so many years ago, written, to put it mildly, by an ebullient personality.

Child Psychiatric Techniques: Diagnostic and Therapeutic Approach to Normal and Abnormal Development Through Patterned, Expressive and Group Behavior. Lauretta Bender, B.S., M.A., M.D., Springfield, Ill., 1952, Charles C Thomas, 335 pages. Price $8.50.

Dr. Bender's book includes the techniques of observation and diagnosis, of care and therapy, developed during more than fifteen years' work with disturbed children at Bellevue Hospital. The approach is oriented about a formulation which integrates Gestalt theories of the psychology of perception with cultural and organic considerations, with the concept of the body image as a focus. The core thesis is that each individual's progressive struggle to attain reality involves not only emotional relationships, but physical relationships as well. Thus, the patterns of perceiving objects and of expressing impulses utilized by the individual in the interaction with space and gravity are of signal significance in the development of the body image.

The importance of the role of form, or technique as exemplified by the patterns of expression in motility, art, and play, is underscored. Form is regarded as a reflection of the psychophysiological maturation level, and a guide to the intellectual development of the child. Difficulty in patterning behavior in the perceptual, motor, and emotional spheres decreases the tolerance of the child for frustration, and increases the need for affectionate care and guidance.

Dr. Bender has filled her book with a wealth of documented case histories, long-term follow-ups, and drawings by the children, all analyzed from a unique conceptual viewpoint. In the field of art, which is discussed at considerable length, the author reveals the most satisfying insights in an impressively complex area. The interpretations of the drawing of the Bender Visual-Motor Gestalt Test are fully illustrated and explained.

A short survey of the current techniques in child psychiatry in the light of their historical backgrounds and recent formulations is followed by a discussion of the author's own concepts with an emphasis on the value of a diagnostic and dynamic formulation of the emotional and motivational factors in the behavior problem. Both group and individual psychotherapy have been found to progress more rapidly against a background of school, creative dance, music, puppet shows, and clay modeling.

This book, which includes an excellent bibliography, was designed neither as a comprehensive nor as an introductory text. Many specific areas are explored in detail, and it provides the interested and oriented physician with an unparalleled opportunity to participate in the evaluation of disturbed children.

JUDITH SCHACHTER AND RUTH BAKWIN

Rheumatic Fever, A Symposium. Edited by Lewis Thomas, M.D., Minneapolis, 1952, University of Minnesota Press, 349 pages. Price $10.00.

This collection of interesting reports reemphasizes the inevitable conclusion that the pathogenesis of rheumatic fever is still obscure. Here again there are reports of attempts to produce the lesions of rheumatic fever in animals, and the expected controversy arises as to whether the pathological lesions produced in animals are at all similar to the ones seen in man. There are papers by Stetson and Thomas who attempt to point out the relationship between the pathogenesis of the Shwartzman and Arthus phenomena and human rheumatic fever. There are also two very interesting papers by Maclyn McCarty, "The Biology of Group A Hemolytic Streptococci" and "The Immune Response in Rheumatic Fever," and a comprehensive study by Jones and Blank on "The Natural History of Rheumatic Fever."

A fitting conclusion to this volume, which is worth-while reading, is the remark by Dr. Benjamin Clawson who says, "All I have to do to keep me humble is to look at an Aschoff nodule about once a week, and I'm not so certain about rheumatic fever after that."

GOLDRING

Young Child Can Be Happy in Bed. Cornelia Stratton Parker, New York, 1952, Thomas Y. Crowell Co., 275 pages. Price $2.95.

This is a discussion of 200 ways to entertain the bedridden child. The text contains much detailed information as to methods and materials. One chapter lists the methods by ages. It is a book the pediatrician might well keep in mind when he finds it necessary to keep a child in bed for some time, as the entertainment of the child is most important to his happiness and this in turn to the rapidity and rate of convalescence.

Editor's Column

THE GAMMA GLOBULIN POLIO PROBLEM

THE recent report of the use of Red Cross gamma globulin for the prevention of polio records one of the most interesting mass experiments in medical history.* In three areas where polio was prevalent approximately one-half of a total of 54,772 children between the ages of 1 and 11 years were given gamma globulin, while the other half serving as a control were given gelatin. The material for injection was so packaged that neither the parents nor the team giving the injection knew which of the two was given to a particular child.

In evaluating the results only paralytic cases were considered, as the diagnosis of nonparalytic polio is too uncertain, and the incidence of transmission could be considered the same for the two groups. The final results showed a smaller number of paralytic cases developing for a period of four weeks beginning seven days after the injection of globulin. This is shown in the following table constructed from the figures in the report.

NUMBER OF CASES DEVELOPING PARALYTIC POLIO

PERIOD AFTER INJECTION	GAMMA GLOBULIN	GELATIN
First seven days	12	16
Second week	3	23
Third week	2	8
Fourth week	1	4
Fifth week	0	3
	6	38
Sixth week	3	4
Seventh week	3	4
Eighth week	1	0
Ninth week	1	1
Tenth week plus	0	1
	8	10
Total after the first seven days	14	48

While there is little difference between the two groups in the first or after the fifth week following the injection, the difference in the four-week period, the second through the fifth week, is statistically significant. In the group receiving gamma globulin about 1 in 4,500 developed paralytic polio in this period, as contrasted with 1 in 720 of the control group receiving gelatin.

The conclusion can be drawn that gamma globulin is of value in the prophylaxis of polio. Further, that in the dosage used in the study it does not give complete protection, that it seemingly is of little use if the disease has been contracted at the time the globulin is given, and that protection is lost after five weeks, as is generally considered to occur when globulin is used in the prophylaxis of measles. Thus there are definite limitations to its value.

There is a cloudy side to the picture. The widespread publicity which has been given to this study by the press, weekly magazines, and over television and radio have created a difficult problem with which the physician will be faced this coming summer when the polio season comes round. It is the quantity of gamma globulin that will be available contrasted with the tremendous demand that will occur.

*Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis. I. Plan and Pilot Study in 1951 (Hammon, Coriell, and Stokes, Jr.); II. Texas and Iowa-Nebraska Studies in 1952 (Hammon, Coriell, and Stokes, Jr.); III. Report of Results (Hammon, Coriell, Wehrle, Klimt, and Stokes, Jr.), J. A. M. A. 150: 739, 750, 757, 1952.

Only gamma globulin from pooled serum is considered to be of value in polio prophylaxis, and the Red Cross blood banks are the only source of large quantities of gamma globulin from pooled sera. A relatively small amount made from placental blood is available commercially at a retail cost of around $6.00 for a 2 c.c. unit. In their fiscal year ending June 30, 1952, the Red Cross obtained 4,121,200 pints of blood in its fifty-seven blood banks (now sixty-one). Sixty per cent of this went to the Armed Forces and 40 per cent for civilian needs. Roughly 50 per cent of the blood was used in the form of whole blood in civilian hospitals or shipped to the Armed Forces, and 50 per cent was processed. By far the larger part was processed into plasma for use by the Armed Forces or stored for disaster relief, and only a small part fractioned. It is from the latter that gamma globulin is obtained. From a pint of whole blood an average of only 7 c.c. of gamma globulin can be obtained.

The dosage of gamma globulin used in the study depended on the weight of the child and it was given in doses of 4, 7, and 11 c.c. Assuming an average dose of 7 c.c., it required 190,000 c.c. of gamma globulin to immunize the 27,000 children, and this required the donations of 27,000 pints of blood. We have been informed that at the end of the summer the Red Cross had only 400,000 2 c.c. units in reserve, or only enough to give one average 7 c.c. injection to around 115,000 children. The child population in the United States 1 to 14 years of age is over 35 million.

In December the Red Cross announced that at the request of the Office of Defense Mobilization it would make an appeal for the donation of 2 million additional pints of blood to be processed into gamma globulin in 1953 for use in polio prophylaxis. Its success will depend not only on a 50 per cent increase in blood donations over the past year, but on obtaining $7,000,000 additional funds in their annual March campaign to help meet the cost. There is no income from the gamma globulin, as Red Cross blood and its products are never sold. Assuming that the 2 million additional pints of blood are obtained and that more of the regular blood is processed into albumin and gamma globulin than in the previous year, somewhere between only 2 and 3 million children can be given one prophylactic injection in 1953. It is likely that the quantity of gamma globulin available will fall considerably short of this figure.

The allocation and distribution of this limited supply of gamma globulin will not be undertaken by the Red Cross. It will be allocated to meet epidemic needs by the Office of Defense Mobilization upon the advice of the National Research Council. Past experience indicates that polio will reach epidemic proportions in 150 counties next summer and that at least 2 million children will be exposed in these counties. So it is obvious that Red Cross gamma globulin will not be generally available to physicians throughout the country. Cases of polio, however, will break out in many hundreds of communities. We can be certain that whenever this happens there will be a wild clamor for gamma globulin arising in each one, as no one can foretell whether or not the first

few cases herald the beginning of an epidemic. The demand moreover will not be limited to one for use in childhood. We know of an instance last fall where gamma globulin was given to thirty-three members of an adult football team following the development of paralytic polio in a member of the squad.

For several years the Red Cross has distributed gamma globulin gratuitously through state and local health agencies for its proved value in measles prophylaxis and modification, and for infectious hepatitis. We have learned that the Red Cross is discontinuing this method of distribution to physicians. The Office of Defense Mobilization, recognizing that a limitation of its use to polio might lead to an increase in measles morbidity and the severity of measles complications to an extent that would outbalance the good that will come from its use in polio, in planning the allocation of gamma globulin has given first priority to the requirements for measles and infectious hepatitis.

The only direct objection we have heard expressed against the use of gamma globulin in polio is that it might prevent the development of the active immunization against polio which is thought to develop in many children when polio is prevalent in the community. Some feel the number of children who gain immunity from nonclinical polio infection tremendously outnumbers those in whom the disease presents definite clinical symptoms. These are theoretical concepts. Not only has it not been proved that children who receive prophylactic gamma globulin cannot develop an active immunity, but it has been suggested that its best use may eventually be in combination with a vaccine, so that an active immunity will be produced under the protective effects of the gamma globulin.

It is not the purpose or thought behind this editorial to criticize the scientific importance of the polio study. It is rather to present the problems that have arisen from its success, and to point out that the physician can expect trouble this coming summer if polio breaks out in his community. Parents quite understandingly will clamor for gamma globulin in view of the widespread publicity the experiment has obtained. It is going to be hard to have to say many times, "None available," and explain the situation that is certain to happen. Physicians can be of great help in obtaining donors by pointing out to parents requesting gamma globulin for their children the necessity for donating blood to the Red Cross. Few will hesitate to contribute to the supply of gamma globulin by giving a pint of their own blood when the situation is explained to them by their physician.

The solution of polio prophylaxis lies in the development of a vaccine for active immunization rather than temporary passive immunization from gamma globulin. While waiting for the development of a vaccine, it would seem that what is most needed is a practical test, analogous to the Schick test, for separating the immune from the nonimmune children, so that the limited supply of gamma globulin will not be wasted. Neither is available despite the tremendous amount of research that has been done in this field.

INFANT DEATHS FROM ASPIRIN

CONSIDERABLE publicity was recently given to three infant deaths from aspirin poisoning in the space of a few weeks in St. Louis. As these were coroner's cases they received local publicity which was picked up by national press services. *These were not accidental cases of salicylate poisoning but therapeutic deaths.* Accidental poisoning from aspirin in runabout and older children is quite common, and probably every large children's hospital service sees a number of cases a year. Fortunately only a few of these are fatal, as by prompt treatment the salicylate intoxication can be rapidly neutralized. It is quite a different story when poisoning occurs from aspirin given to a young baby to "bring down a fever."

On Nov. 4, 1952, an infant 6 months of age was admitted to the Children's Hospital with convulsions from aspirin poisoning, who died six hours after admission. The story was that for four days she had been given a half aspirin tablet every few hours for an infection—a total of 50 grains. The blood salicylate level was 56 mg. per cent.

On November 5, a 2½-month-old infant was admitted who died ten hours after admission. During the twenty-four hours before hospitalization she received 25 grains of aspirin. The blood salicylate level was 26.4 mg. per cent.

The third case was a 4½-month-old infant admitted November 16, who died ten hours after admission. She had been given two 5 grain tablets of aspirin rectally, and enough 1¼ grain tablets orally to make a total of 27 grains in the twenty-four hours previous to admission. The blood salicylate level was 47 mg. per cent.

While three deaths in young infants from aspirin poisoning admitted to the same hospital in a moribund condition in a space of twelve days is most unusual, and the chances are will not happen again, their occurrence vividly dramatizes the danger of the use of aspirin for therapeutic purposes in young infants.

Parents who read the numerous advertisements or listen to the radio commercials extolling this or that brand of aspirin for children can hardly be expected to know they are dealing with a drug potentially lethal for young infants. Physicians should know better, but in two of these three cases the aspirin had been prescribed by an osteopathic physician. If a physician once prescribes even small doses of aspirin for a baby, the chances are the parents will use it again without consulting the physician and without realization of this ever-present danger of overdosage.

The physician has an opportunity to practice good preventive pediatrics by warning parents never to give aspirin to a baby, and the necessity of keeping the household bottle of aspirin tablets out of the reach of young children. The danger of "accidental" aspirin poisoning has increased with the introduction of candied and flavored preparations widely advertised "for children." It would be more accurate to designate cases of poisoning from this or that drug left where children can reach it as "poisoning due to parental carelessness," rather than "accidental poisoning."